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VOLUME 29 MARCH, 1925 NUMBER 3

THE PEROXIDASE REACTION IN EPIDEMIC ENCEPHALITIS

A NEW DIAGNOSTIC AND PROGNOSTIC METHOD *

AKIRA SATO, M.D., AND SH. YOSHIMATSU, M.D.

SENDAI, JAPAN

This report concerns a characteristic feature of the blood picture of epidemic encephalitis which, we believe, will prove extremely valuable in diagnosis and prognosis. Limitation of available clinical material and in ability to explain some features of our work have prevented an earlier presentation of the facts. However, the results of a series of animal experiments carried out by one of us [1] recently have substantiated the clinical evidence assembled two years ago. Briefly, this evidence can be summarized: The peroxidase test (copper method) of Sato and Sekiya on myeloid leukocytes is negative in an acute case of typical epidemic encephalitis (with lethargy, ophthalmoplegia, and asthenia or fever), but is positive in any other disease, whether of infectious or non-infectious origin. This is true only of the peroxidase test as done by the copper method, which we believe is superior to other peroxidase methods in simplicity, in sensitivity, in constancy of color and its contrast with the unstained red cells, and in the durability of the reagents used. Moreover, fixation of the blood smears is unnecessary.

PEROXIDASE STAIN OF SATO AND SEKIYA (COPPER METHOD)

I. Reagents Used.

1. Solution A. Copper sulphate solution, one half per cent.

2. Solution B. Preparation: Rub 0.2 gm. of benzidin with a few drops of water in a mortar. Add 200 c.c. of water at room temperature and filter. To the filtrate add 4 drops of hydrogen peroxid (3 per cent.). If kept in a brown bottle in the dark when not in use, this preparation will last a year, although precipitation will begin to occur soon after preparation.

* Received for publication, Dec. 31, 1924.

* From the Department of Pediatrics, The Medical College, the Tohoku Imperial University.

* Preliminary paper read before the Forty-Sixth Regular Meeting of the Tohoku Medical Association, May 20, 1922, entitled: Characteristic Feature of Lethargic Encephalitis.

1. Sato, A.: The Localization of a Lesion in the Brain by Differential Staining of Blood Smears (Preliminary Report), this issue, p. 313.

3. Solution C. (counter stain).

(*a*) Safranin, aqueous solution, 1 per cent, or (*b*) Neutral red, or (*c*) Carbolfuchsin (one part in five). Safranin is by far the best of these counter stains.

II. Method Used.

To a fresh, dry blood smear apply Solution A. Pour off most of it and apply Solution B for two minutes. Then wash thoroughly with water. The peroxidase granules of the leukocytes are stained a deep bluish green, which does not fade. The smear may be preserved mounted in cedar oil, or unmounted. In certain cases, Dr. Ohara applied Solution B for only twenty seconds, a fact which demonstrates the sensitiveness of the copper method. For counterstaining do not rinse after pouring off the peroxidase stain, but add Solution C at once and let stand for two minutes before washing.

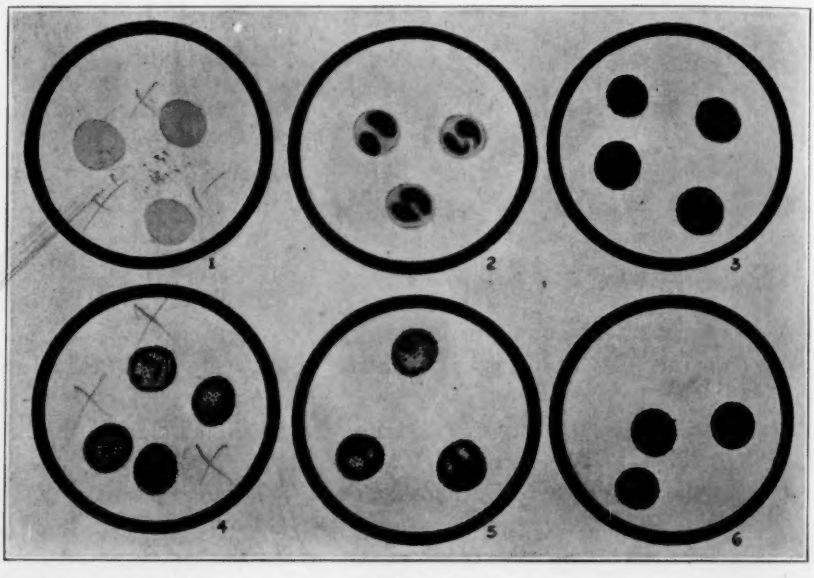

Fig. 1.—Blood smears (only myeloid leukocytes represented): 1, 2 and 3, blood smears of acute typical lethargic encephalitis; 4, 5 and 6, control specimens.

Peroxidase reaction (copper method)		*Oxidase reaction (Winkler-Schultze)*
1. Peroxidase-negative	2. Peroxidase-negative (nucleus stained with safranin)	3. Oxidase-positive
4. Peroxidase-positive	5. Peroxidase-positive (nucleus stained with safranin)	6. Oxidase-positive

The cytoplasm of the myeloid leukocytes is stained blue by this method, whereas the lymphoid elements show no trace of blue or green but appear red because of their red-staining nuclei. It should be added here that copper salts, especially copper sulphate, were found by Dr. Suzuki to be superior to any other salts.

In an endeavor to find a simple substitute for the oxidase reaction of Winkler and Schultze, in which simple, durable reagents could be used, Sato and Sekiya devised this peroxidase reaction. With the oxidase reaction, in which indophenol blue is the basis, the leukocytes become indigo blue, whereas with the peroxidase reaction, as described, they become greenish blue (Fig. 1). Blood smears from every available case on our pediatric service were stained by this new copper method. The results proved entirely satisfactory until we examined a smear from a typical case of acute epidemic encephalitis (M.I.). To our great surprise the blood failed to take the stain, in contrast with all cases previously examined. Another typical case (E.K.) yielded a similarly negative result. This finding was constant on all smears taken from these two patients, although possible defects in the reagents and cover slips used were ruled out by series of controls. Now for the first time we suspected the presence of some peculiar property in the blood from cases of acute epidemic encephalitis. But even yet we questioned the findings, since the oxidase reaction was positive not only in cases of every variety but also in these two cases of encephalitis. All doubt was dispelled by results obtained from a series of experiments, which are described below.

CASE HISTORIES

CASE 1.—E. K., a boy, was admitted on the thirteenth day of illness, complaining of drowsiness and high fever. The initial symptom had been diplopia, which was followed after two days by headache, drowsiness, delirium and twitching of the extremities. Nine days later the intense drowsiness and high fever were the most prominent features. Other findings were ptosis, especially on the left, and slight rigidity of the extremities. Ophthalmoscopic examination was negative. Twitching of muscles of the face and trunk soon appeared, the cerebral symptoms increased, and death on the eleventh day after admission was hastened by secondary pneumonia.

Examination of the cerebrospinal fluid on three occasions revealed it to be clear; under a pressure of 140 to 200 mm. of water; with the Nonne, Pandy and Boveri reactions negative, and with sugar present. Microscopic examination showed a small number of lymphocytes, and bacteriologic examination showed absence of organisms. At necropsy, diffuse pial hemorrhages at the base of the brain were found, and microscopically numerous particles like brain-sand in the lenticular nucleus especially, and minute necrotic areas in the ventral portions of the corpora quadrigemina.

CASE 2.—M. I., a boy, was admitted on the fifth day of illness, complaining of drowsiness and high fever. The initial symptom had been insomnia, lasting for two days, followed by diplopia, ptosis, drowsiness, dysphonia, bradykinesis and convulsions. Other findings were ptosis, twitching of both hands and clonic spasms of all extremities. Ophthalmoscopic examination was negative on the left, but showed slight blurring of the optic disc on the right. One week after admission he seemed better and the somnolence was disappearing. Improvement continued but as sequelae slightly irregular respiratory rhythm and choreiform movements of the body developed.

Examination of the cerebrospinal fluid on two occasions revealed the presence of 160 to 180 mm. of water; with the Nonne, Pandy and Boveri reactions very faintly positive on the first examination but negative on the second; with a few lymphocytes and on culture no bacterial growth.

TABLE 1.—*Peroxidase Reaction (Copper Method) and Oxidase Reaction (Winkler-Schultze) (Staining two Minutes with Solution B)*

Blood	Boy E. K., 14 Years Old			Boy M. I., 9 Years Old			Control Specimens Tested at the Same Time	
	Day of Disease	Peroxidase	Oxidase	Day of Disease	Peroxidase	Oxidase	Peroxidase	Oxidase
First examination...	15th (39 C.)	—	+	6th (38.6 C.)	—	+	+	+
Second examination.	20th (39.5 C.)	—	+	15th (38.2 C.)	—	+	+	+
Third examination...	23d death (on necropsy)	—	+	18th (37.6 C.)	+	+	+	+
Later examinations...				Specimens, later taken after intervals of about 1 week	+	+	..	..

It is clear now that the peroxidase reaction (copper method) is negative in typical cases of acute epidemic encephalitis, but that it is positive in convalescent cases. Hence it appears that the reaction may be an index of the course of this disease. Further proof of this developed when we varied the staining time of Solution B, Solution A remaining constant, because in blood smears from the second case taken on the fifteenth day of the disease we were able to change the reaction from negative to positive by prolonging the staining time. In spite of this prolongation, some remain negative. The results in detail appear in Table 2.

TABLE 2.—*Peroxidase Reaction (Copper Method). Result of Prolonged Staining*

Blood Day of Examination (Same as in Table 1)	Boy E. K. Staining Time of Solution B			Boy M. I. Staining Time of Solution B		
	2 Minutes	10 Minutes	30 Minutes	2 Minutes	10 Minutes	30 Minutes
First examination.....	—	—	—	—	—	—
Second examination.....	—	—	—	—	+	Not tested
Third examination.....	—	—	—	+	Not tested	Not tested

Since we had established the existence of this negative peroxidase reaction (C.M.) in cases of typical acute encephalitis, it became necessary to examine blood smears from every other possible pathologic condition, in order to ascertain the possibility of its presence in other diseases.

1. CHRONIC STAGES OF EPIDEMIC ENCEPHALITIS

Since the peroxidase reaction (C.M.) changes from negative to positive during recovery from an attack of acute encephalitis, one expects a positive reaction in cases exhibiting the sequelae of this disease. Table 3 confirms this expectation. In a word, the peroxidase reaction (C.M.) is equally positive in cases showing the sequelae of encephalitis and in normal, healthy persons.

TABLE 3.—*Blood Smears and Reactions*

Blood Smears in Chronic Epidemic Encephalitis	Peroxidase Reaction (Copper Method)	Oxidase Reaction (Winkler-Schultze)
1. Child with choreiform movements after acute epidemic encephalitis	+	+
2. Child recovered from acute attack, with lethargy as only sequel	+	+
3. Adult, recovered from acute attack, with excessive lethargy as only sequel	+	+
4. Child, recovered from acute attack with slight lethargy as only sequel	+	+
5. Child with motor and mental disorders after acute epidemic encephalitis	+	+

2. ACUTE INFECTIOUS DISEASES

TABLE 4.—*Peroxidase Reaction in Acute Infectious Diseases*

Disease	Peroxidase Reaction (Copper Method)	Oxidase Reaction (Winkler-Schultze)
Measles (acute stage)	+	+
Scarlatina (acute stage)	+	+
Varicella (acute stage)	+	+
Diphtheria of pharynx and larynx (acute stage)	+	+
Typhoid fever (acute stage)	+	+
Paratyphoid B (acute stage)	+	+
Dysentery (acute stage)	+	+
Influenza (acute stage)	+	+
Whooping cough (convulsive stage)	+	+
Vaccinia (eruption with fever)	+	+
Lobar pneumonia (acute stage)	+	+
Tetanus	+	+
Acute miliary tuberculosis	+	+
Sepsis (Staphylococcus pyogenes flavus)	+	+
Sepsis (influenza bacillus)	+	+
Sepsis (meningococcus)	+	+
Sepsis (unknown organism)	+	+

Evidence assembled in Table 4 fails to demonstrate any acute infectious disease in which the peroxidase reaction (C.M.) is negative. The intensity of the reaction is the same as in healthy children.

3. ACIDOSIS

Many patients in which acidosis was present, as in infantile diarrhea, and "yekiri" (Japanese name for bacillary dysentery), and nephritis, all gave positive peroxidase reactions (C.M.) of the same intensity as normal persons, as well as positive oxidase reactions.

4. DISEASES OF THE CENTRAL NERVOUS SYSTEM WITH SOMNOLENCE

TABLE 5.—*Peroxidase Reaction (Copper Method) in Severe Diseases of the Central Nervous System with Somnolence*

Disease	Peroxidase Reaction (Copper Method)	Oxidase Reaction (Winkler-Schultze)
Tuberculous meningitis	+	+
Acute purulent meningitis (meningococcus)	+	+
Acute purulent meningitis (pneumococcus)	+	+
Acute purulent meningitis (Streptococcus mucosus)	+	+
Acute purulent meningitis (Bacillus influenzae)	+	+
Acute purulent meningitis (unidentified bacillus)	+	+
Acute influenzal encephalitis (acute stage), clinically quite different from epidemic encephalitis	+	+

Epidemic encephalitis thus is different from these other forms, however similar they may be clinically (Table 5).

5. OTHER DISEASES

Similar positive peroxidase and oxidase reactions were obtained in all the diseases enumerated below:

(*a*) Diseases of the nervous system: general paralysis, syphilitic meningitis, lead encephalitis, acute purulent and serous meningitis not affecting consciousness and Landry's paralysis; poliomyelitis, epilepsy, brain tumors, paralysis agitans, chorea and mental deficiency.

(*b*) Diseases of the endocrine system; cretinism, diabetes insipidus, Addison's disease and hypophyseal cyst with precocious puberty.

(*c*) Diseases of the digestive system: different forms of gastro-intestinal indigestion, infantile beri-beri, duodenal ulcer, stomatitis, pharyngitis, acute appendicitis, acute peritonitis, intussusception, syphilitic hepatitis, catarrhal jaundice, cancer of stomach, intestinal parasitosis and hernia.

(*d*) Diseases of the respiratory system: rhinitis, laryngitis, tracheitis, bronchitis, bronchopneumonia, bronchiectasis, gangrene of lung, pleurisy, empyema, tuberculosis, otitis media and acute mastoiditis.

(*e*) Diseases of the blood: anemias, leukemia, myeloid chloroma, aplastic anemia, the splenomegalies (including Gaucher's disease).

(*f*) Miscellaneous diseases: nephritis, pyelonephritis, abdominal tumors, acute and chronic heart disease, congenital syphilis, surgical tuberculosis and paroxysmal hemoglobinuria.

Thus we may conclude that the peroxidase reaction (C.M.) on the myeloid elements of the blood is always positive in every type of disease, however severe the intoxication, except in acute epidemic encephalitis.

The question arose whether blood examined at necropsy gave as reliable results as that during life. The third blood examination on the first case (C.M.) of the acute encephalitis series was made at necropsy, and the peroxidase reaction was found negative. Many of the smears made from the patients before mentioned were obtained both before and after death (all within forty-eight hours of death), but the results were constant in either event. Unfortunately, the first case is the only peroxidase negative instance which we have been able to study after death. No data have been obtained on the validity of blood smears made longer than forty-eight hours after death. The blood of experimental animals after death is useless because of early putrefaction.

If the peroxidase and the oxidase reactions had been considered of a similar biologic significance and only the latter studied, this characteristic finding in acute encephalitis would have been overlooked. One might attribute it to a difference in sensitiveness of the two reactions. This is not true, however, as shown by the following facts:

1. There is no appreciable difference between the intensity of the peroxidase and of the oxidase reactions in the diseases before mentioned, except in acute encephalitis.

2. The peroxidase reaction is very sensitive because of the presence of copper sulphate.[2] Hence Ohara considered that staining with Solution B for two minutes was too long, and shortened the time to twenty seconds, further emphasizing its sensitiveness.

3. The peroxidase is more specific than the oxidase reaction, for the former does not stain fat and the latter does.

4. Sato's [1] animal experiments. By puncturing the brain of a rabbit at two points, in the corpus striatum on each side, Sato was able to produce a change in the myeloid elements of the blood similar to that found in acute epidemic encephalitis, namely, negative to the peroxidase reaction (C.M.) and positive to the oxidase reaction. He designated this the peroxidase puncture. It is always bilateral, in contrast to other known punctures, such as heat puncture or sugar puncture. It seems probable that the peroxidase and the oxidase reactions, although apparently very similar, are regulated by different nerve centers, the center for the peroxidase reaction being located at the point of the peroxidase puncture. Sato has been unable to produce similar results so far by the use of drugs.

BLOOD PICTURE IN ACUTE EPIDEMIC ENCEPHALITIS

The literature concerning the blood picture found in encephalitis is so conflicting that a summary of the principal reviews and reports on the subject will be attempted.

The Association for Research in Nervous and Mental Diseases.[3]—Normal values for red blood count and hemoglobin. Leukocyte counts varying from 4,500 to 32,000, with an average of 12,000. Figure 2 shows these relations in graphic form, and Figure 3 the percentages of polymorphonuclear leukocytes. These two figures serve to emphasize the extent of variation in the different stages of the diseases.

Felix Stern,[4] in his review of the literature, says that the blood picture was found normal by Strümpell and Nonne; leukocytosis by Pribam, Géronne, Dimitz, Gröbbels (with a lymphocytosis), Siegenbeck; lymphocytosis by Luzzatto and Rietti, Sabatini, Schupfer,

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2. Suzuki, K.: On the Influence of Different Salts on the Peroxidase Reaction (in press).

3. Acute Epidemic Encephalitis. An Investigation by the Association for Research in Nervous and Mental Diseases. Report of the Papers and Discussions at the Meeting of the Association; New York City, 1921, pp. 91-93.

4. Stern, F.: Die epidemische Encephalitis, Berlin, J. Springer, 1922, pp. 228.

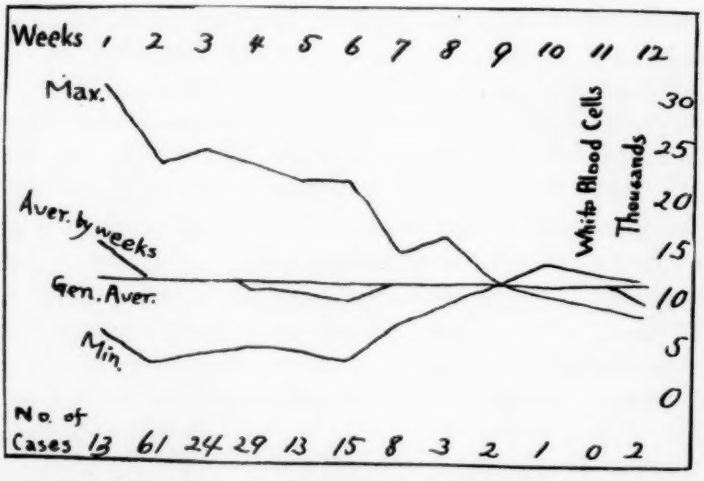
Weeks 1 2 3 4 5 6 7 8 9 10 11 12
Max.
Aver. by weeks
Gen. Aver.
Min.
White Blood Cells Thousands
30 25 20 15 10 5 0
No. of Cases 13 61 24 29 13 15 8 3 2 1 0 2

Fig. 2—The leukocyte count in epidemic encephalitis, as reported by the Association for Research in Nervous and Mental Diseases.

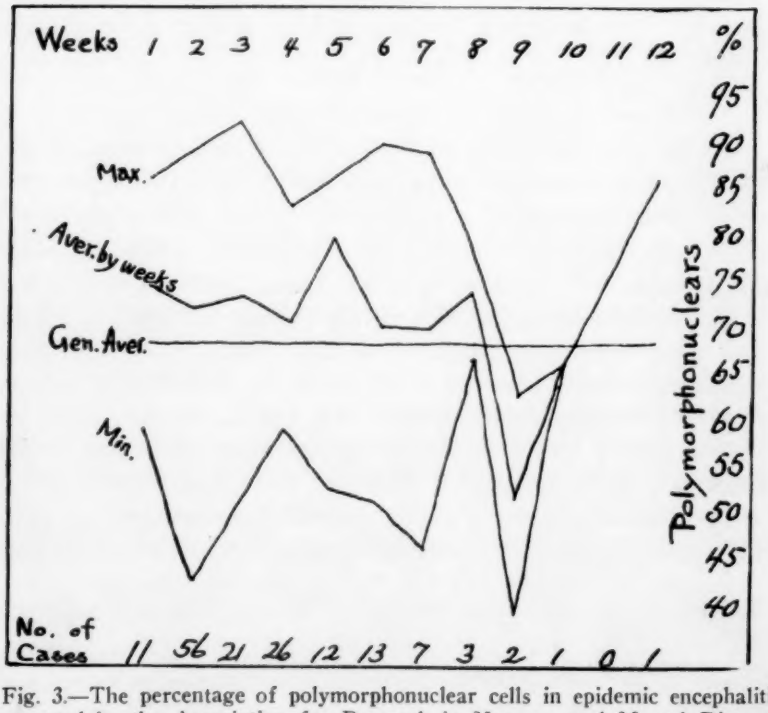

Fig. 3.—The percentage of polymorphonuclear cells in epidemic encephalitis, as reported by the Association for Research in Nervous and Mental Diseases.

Alexander and Allen. In twenty cases Vaidya noted an average of 8,000 to 9,000 leukocytes. According to Moritz, all types of blood pictures may be present. Stern adds that no blood picture can be indicative of the part of the brain affected, and that in spite of the confused findings, a leukocytosis is of some value in differentiating encephalitis and influenza, typhoid or some mental diseases. A lymphocytosis is not a characteristic feature.[5]

Huss [6] analyzed seventeen cases. The white cell count is usually normal or a little decreased. Moderate leukocytosis occurs in some cases (none above 15,000). During the early febrile stage the leukocyte count falls to about 5,000, but later in the course of the fever or after defervescence rises quickly. In fatal cases there is a progressive moderate leukocytosis. A lymphocytosis of from 30 to 50 per cent. is the rule.

Von Economo [7] concludes that there is no characteristic blood picture. In the acute stage, encephalitis shows the same moderate leukocytosis as in many other infectious diseases.

Reports have been published in the Japanese literature by Tatsukichi Irisawa [8] who reviews seven cases. Leukocyte count is usually normal, only twice above 20,000. Lymphocytosis may appear. Eosinophils are slightly decreased.

Susumu Hoshino [9] reviews six cases and finds a normal picture in three of them.

Shô Naito [10] reviews five cases, and reports an average white count of 9,000, neutrophil percentage of from 70 to 80, with slightly decreased lymphocytes, and slightly increased eosinophils.

In a word, although some authors attribute certain features to the blood of encephalitis, while others detect no typical picture, nothing pathognomonic in the blood from such a case could be found. Leukocytosis, lymphocytosis, mononucleosis or decrease of eosinophils occur in many other diseases, and none of these pictures, of course, can lead to the clinical diagnosis of any disease. The copper peroxidase reaction, on the other hand, is pathognomonic of the typical case of acute epidemic encephalitis, so that by the study of a blood smear alone one can diagnose this condition. Some other disease may yet appear which we have not tested and which may give a peroxidase negative reaction, such as

5. Stern, F.: Pathogenetische Probleme der epidemischen Encephalitis, Klin. Wchnschr. **1**:433, 1923.

6. Huss, R.: Einige Beobachtungen über die Leukozytenzahl bei der Encephalitis epidemica, Wien. klin. Wchnschr. **35**:55, 1922.

7. Von Economo, C.: Encephalitis lethargica, Wien. med. Wchnschr. **73**: 1113, 1923.

8. Irisawa, T.: Zikken-iho, 1920, p. 276.

9. Hoshino, S.: Zikken-iho, 1921, p. 126.

10. Naito, Shô: Tohoku Igaku Zasshi, 1922.

possibly Wilson's disease (especially the terminal stages). But practically it may be said that a blood presenting this picture may be diagnosed as that from a patient suffering from some severe affection of the area of peroxidase puncture of the brain, namely, the corpora striata.

This characteristic blood picture occurs only in a severe condition of the corpora striata. For this reason it does not occur in paralysis agitans, chorea minor or chronic epidemic encephalitis with sequelae, even if these may have affected the areas of peroxidase puncture. No case of Wilson's disease as yet has been available for study.

It is evident that this blood picture, strictly speaking, is not characteristic of the disease acute encephalitis itself but of any stimulus sufficiently strong to arouse the region of peroxidase puncture in the brain, that is, the region which acute encephalitis most strongly affects. Therefore if influenza, poliomyelitis, syphilis, brain tumor or traumatic brain lesion should involve the area of the peroxidase puncture to any extent, the characteristic blood picture theoretically would occur. But such conditions must be rare because the puncture is a bilateral one. To be sure, influenza may affect these areas, but experience shows that even in a severe case of influenza, this blood picture is never produced.

VALUE OF THE PEROXIDASE REACTION

The discovery on a fresh blood smear that all the myeloid leukocytes are peroxidase negative but oxidase positive will be of value in the following respects:

Diagnosis.—It will point to a very serious lesion of the corpora striata. Thus it will be characteristic of the typical form of acute epidemic encephalitis. Only the typical form, with ophthalmoplegia, lethargy and fever, produces this reaction. Many other varieties which do not act on the corpora striata do not produce the reaction.

Prognosis.—If the prognosis in acute encephalitis depends on the intensity of affection of the corpora striata, the peroxidase reaction will be negative while the disease process is progressing, but will become positive (that is, normal) during convalescence. If the reaction is negative when using two minutes in staining with Solution B, increase the staining time to five, ten, fifteen or twenty minutes on other fresh blood smears until the peroxidase granules become well stained. The length of time necessary to stain the granules will be in direct proportion to the serverity of the disease.

The value in prognosis of shortening the staining time of Solution B is not yet clear, because other factors, such as the freshness of the blood smears, the reagents used, and so forth, which might influence the peroxidase reaction, would then predominate and render the result equivocal. Dr. Ohara shortened the time to only twenty seconds.

One must still be more cautious in considering the prognosis in other diseases than acute encephalitis. Severe affection of the corpora striata will occur only in acute epidemic encephalitis, but it is difficult to imagine that in any severe general intoxication or infection these bodies would remain entirely unaffected. This minimal involvement would be too slight to produce any perceptible variation of the peroxidase reaction. The following scheme depicts the course of the peroxidase reaction during a disease.

Differential Diagnosis.—It will aid in differentiating acute epidemic encephalitis and other similar acute diseases, such as tuberculous meningitis, poliomyelitis, acute meningitis, and influenzal encephalitis.

Forensic Matters.—A peroxidase reaction on heart's blood from a cadaver will aid in determining the cause of death. So far, the blood from no patients dead for more than two days has been examined.

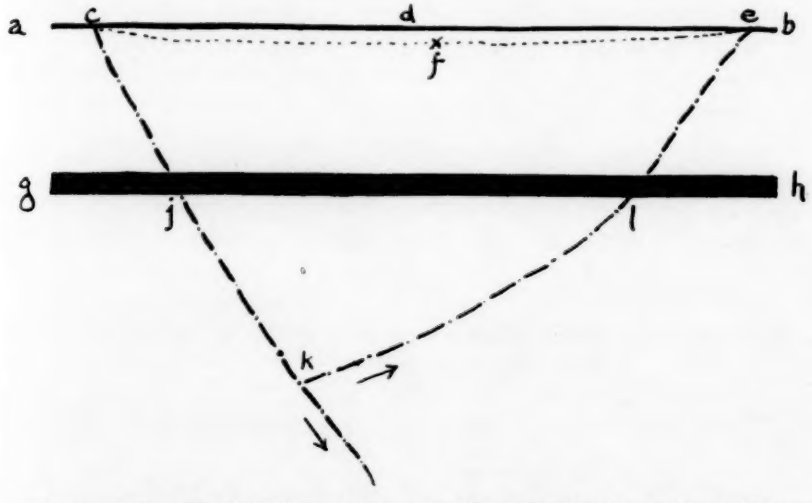

Fig. 4.—Below the thick line (g-h) peroxidase reaction is negative with two minutes staining time, but above is positive; while the point f, for instance, will not show any modified reaction (even with shortened time). Intensity of peroxidase reaction (copper method), on myeloid leukocytes: a c d e b, black line, in normal human blood; c f e, dotted line, in a disease of general severe infection, for instance; c j k j l e, dot and dash line, in typical lethargic form of acute epidemic encephalitis.

CONCLUSIONS

1. The peroxidase reaction (copper method) of Sato and Sekiya on fresh blood smears is negative (that is, all the myeloid leukocytes fail to take the stain) in typical cases of acute epidemic encephalitis, but is positive (that is, all the myeloid leukocytes take the stain) in every other disease.

2. During convalescence from encephalitis, the reaction changes from negative to positive.

3. The oxidase reaction of Winkler and Schultze on myeloid leukocytes of the blood is always positive in all diseases, including acute epidemic encephalitis.

4. Animal experiments have located the brain area controlling the peroxidase reaction in the corpora striata, puncture of which or severe inflammation of which, as in typical acute encephalitis, produces a negative peroxidase reaction.

5. In prognosis, the peroxidase reaction is valuable, being more favorable when positive and less favorable when negative. The length of staining time with Solution B necessary to produce a positive reaction is directly proportional to the gravity of the prognosis.

THE LOCALIZATION OF A LESION IN THE BRAIN BY DIFFERENTIAL STAINING OF BLOOD SMEARS

PRELIMINARY REPORT *

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SENDAI, JAPAN

In the past, there has been no method of localizing lesions in the brain except by a careful mental and physical examination of the patient. No purely laboratory finding which might lead to such localization has been described. Changes in the blood, characteristic of injuries to certain parts of the brain, have not been recorded. Stern [1] argued against the possibility of such characteristics by pointing out that there was no relation between the degree of change in the blood picture and the degree of cerebral damage. Moreover, even if it were possible to produce a definite change in the blood picture (such as an eosinophilia) by experimental injury of a certain part of the brain, it would by no means follow that a patient presenting such a blood picture must necessarily have a lesion of this part of the brain.

In another paper, published in this issue, Yoshimatsu and I have pointed out a change in the blood (as tested by the peroxidase reaction) which occurs in lethargic encephalitis (Table 1). From this table one may conclude that:

TABLE 1.—*Reaction of the Myeloid Leukocytes in Fresh Blood Smears to the Peroxidase Stain (Copper Method)*

Acute lethargic encephalitis	Negative
Other diseases (including acute infections, toxic diseases, and affections of the central nervous system)	Positive

1. The peroxidase reaction (copper method) probably has no relation to disease of the brain in general, for it is negative only in epidemic encephalitis.

2. The reaction probably has no relation to inflammation, infection or intoxication, as it remains positive in many such diseases.

3. The negative reaction may be characteristic of acute lethargic encephalitis.

* Received for publication, Dec. 31, 1924.

* From the Pediatric Department of the Medical College of the Tohoku Imperial University.

* Read before the Twenty-Ninth Annual General Meeting of the Japanese Pediatric Society, Fukuoka, April 27, 1924.

1. Stern, F.: Die epidemische Encephalitis, Berlin, J. Springer, 1922, pp. 228.

In striking contrast to this stands the reaction of the myeloid leukocytes to the oxidase stain (Winkler-Schultze), in which the granules do not lose their ability to stain positively in epidemic encephalitis. This brings us face to face with two problems: (1) Why does peroxidase reaction (copper method) become negative in acute epidemic encephalitis? (2) Is there a biologic difference between the peroxidase granules and the oxidase granules of the myeloid leukocytes?

RESULTS OF ANIMAL EXPERIMENTATION

In an attempt to throw some light on these problems, a number of brain injuries were produced experimentally in rabbits and the effect on the reaction of the myeloid leukocytes to the peroxidase and oxydase stains noted. These results have been summarized in Table 2. It is seen that only those rabbits which had received a bilateral injury of the corpora striata showed a peroxidase negative reaction with the blood. I have, therefore, named this injury "peroxidase puncture."

TABLE 2.—*Reaction of Myeloid Elements of Fresh Blood Smear of Rabbit*

Main Sites of Injury	Peroxidase Reaction (Copper Method)	Oxidase Reaction (Winkler-Schultze)
Corpus striatum, bilateral	−	+
Corpus striatum, unilateral	+	+
Corpora quadrigemina, bilateral	+	+
Parts before ventriculus lateralis, bilateral	+	+
Parts over ventriculus lateralis, bilateral	+	+
Parts lateral on ventriculus lateralis, bilateral	+	+
Different poisons	+	+

This bilateral puncture of the corpora striata has been tried on thirty rabbits, but because of the experimental difficulties encountered, the result was considered successful in only two. I have been very careful not to consider a blood smear peroxidase negative unless (1) the blood was obtained intra vitam or at least a few moments after death; and (2) the technic for making the stain was rigidly adhered to (Solution B of the copper method must be freshly prepared and applied for two minutes); and (3) a control smear stained by the oxidase method (Winkler-Schultze) gave a positive result. Furthermore, a result was considered negative only when all of the granules in the leukocytes failed to take the peroxidase stain. A mere decrease in the number of peroxidase granules, however marked, was regarded as entirely negative. The blood of dead animals undergoes rapid putrefaction. For this reason a number of animals had to be discarded, as they died during my absence. However, the first indication that I received of a successful "peroxidase puncture" was from a rabbit on which I operated July 4, 1923. This animal was found dead the next morning. Blood smears were then made at necropsy, and showed a peroxidase negative reaction. I have

not regarded this experiment as a successful one, however, as the blood was examined after death.

In making the puncture, the skull of the rabbit is trephined and a Paquelin thermocautery plunged perpendicularly into the corpora striata. In later experiments, a glass tube with suction was used instead of the thermocautery. Injury by means of electricity has not been tried yet.

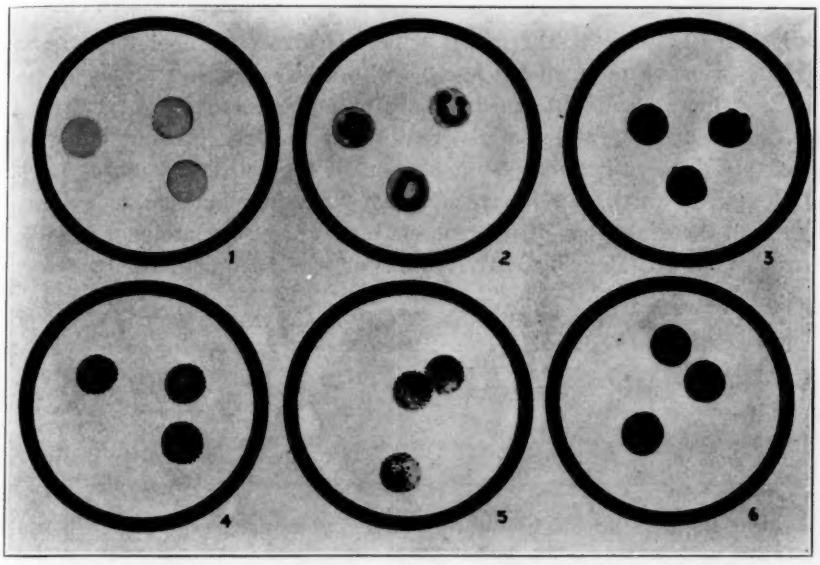

Fig. 1.—Blood smear of rabbits (only myeloid leukocytes represented).

	Peroxidase reaction (copper method)		*Oxidase reaction (Winkler-Schultze)*
"Peroxidase-punctured" animal	1. Peroxidase-negative	2. Peroxidase-negative (nucleus stained with safranin)	3. Oxidase-positive
Control animal	4. Peroxidase-positive	5. Peroxidase-positive (nucleus stained with safranin)	6. Oxidase-positive

After the operation, some time must elapse before the change in the reaction of the leukocytes will take place. In the two experiments which were considered successful, it was three hours and thirty-five minutes with one and four hours with the other before this change had occurred. In a number of animals that died of postoperative shock, the result was without doubt unsuccessful because they did not survive long enough.

COMMENT

It will be seen from the foregoing that there are two conditions under which a blood smear may become peroxidase negative while remaining oxidase positive: (1) clinically, in epidemic encephalitis, and (2) experimentally, by the peroxidase puncture. In both of these conditions there is a bilateral injury to the corpora striata. I have arranged the results in table form (Table 3).

This blood reaction is so specific that it may be utilized for the localization of a lesion in the brain when there is involvement of the corpora striata. Furthermore, such a lesion will not be slight, but rather extensive. A mere needle puncture of both corpora striata will never result in a peroxidase negative stain. The injury must be greater than this. Probably there is injured also a portion of the substantia nigra, Luys' body, and so forth, but I have avoided damaging the dentate nucleus. We will, therefore, have to accept the term corpus striatum in a wider sense, as has been done by Spatz,[2] to include these neighboring structures.

TABLE 3.—*Cause and Character of Disease*

Disease or Experiment	Cause	Character of Lesion	Main Site of Lesion
Acute lethargic encephalitis	Virus	Inflammation	Corpora striata
Peroxidase puncture	Mechanical lesion	Loss of substance	Corpora striata

To limit further the site of the peroxidase puncture, more experimentation and refinements of technic will be necessary. All we can say now is that when the blood of a person reacts negatively to the peroxidase stain and positively to the oxidase stain, that person has a bilateral brain lesion in the region of the corpora striata.

None of the other specific brain punctures which have been described have this reverse application. The "sugar puncture" of Claude Bernard leads to a hyperglycemia and glycosuria, but the occurrence of these symptoms of diabetes mellitus would have almost no significance as indicating a lesion in the brain. Similarly "heat punctures" and "cold punctures" have been recorded, but it is seldom that the subnormal temperature or fever is the result of intercranial injury.

CONCLUSIONS

1. As shown in a previous paper, acute lethargic encephalitis is the only disease in which the myeloid leukocytes in a fresh blood smear show a negative peroxidase reaction (copper method) while remaining positive under the oxidase stain (Winkler-Schultze).

2. Spatz, H.: Das extrapyramidale motorische System, Klin. Wchnschr. **2**:617, 1923.

2. A bilateral puncture of the corpora striata is described which leads to a similar blood picture. This puncture has been named "peroxidase puncture."

3. These facts have a reverse application, namely, a patient whose blood shows this characteristic staining reaction must suffer from a bilateral lesion of the corpora striata.

THE ASSOCIATION OF ANEMIA AND PNEUMONIA IN INFANTS

TREATMENT BY BLOOD TRANSFUSION *

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It is a well established fact that anemic children are prone to infections. Moreover, the course of infections in such children is apt to be particularly severe. It is not uncommon for us to see the same poorly nourished, anemic child returning to the hospital or dispensary repeatedly, with recurrent infections of one or another part of the body. Anemic children are not only more prone to infectious processes but they appear to stand them poorly, and, as we are apt to say, seem to have a lowered resistance.

We have observed a number of such infants, whose general condition was poor and whose blood revealed distinct secondary anemia, stricken with acute infections of the lung. In some, the pulmonary process appeared in the form of bronchopneumonia; in others, as lobar pneumonia. In some, the pneumonia was secondary to an upper respiratory infection, tonsillitis, pharyngitis and otitis; in others, the pulmonary infection appeared to be primary, with the secondary appearance of other infectious foci, notably in the middle ear.

The problem of the treatment of such children is extremely difficult. Even before the advent of the infectious process, they are a therapeutic problem. Proper feeding, hygiene and the administration of iron often have little or no effect. It happens frequently that when we are beginning with difficulty to make some progress in the cure of anemia, another infection takes hold of the child, the result of all our treatment is at once negatived, and if the child recovers from the infection we find the blood conditions even worse than before.

It is in this difficult type of patient that I have seen some remarkable therapeutic results following blood transfusion.

My attention was first drawn to this subject six years ago, when I had occasion to treat a child, aged 2 years, who was suffering from severe rickets and anemia and who developed lobar pneumonia. This child weighed 17 pounds (8,711 gm.), his hemoglobin was only 32 per cent. and the pulmonary infection seemed about to cause his death. (For details see Case 1.) Though there were marked cyanosis, abdominal distention, high fever and respirations of 86 per minute, a transfusion

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* From the Department of Pediatrics, Mt. Sinai Hospital.

of 120 c.c. citrated blood was given. As will be seen in Chart 1, the result was remarkable. There was a sudden drop to normal, followed by a chill and a rise to 106.6 F., and a rapid fall to a permanently normal temperature. The dyspnea subsided, the cyanosis disappeared and the child made an uninterrupted recovery. Five days after the transfusion the hemoglobin was 70 per cent. Since that time, six years ago, it has never fallen below this figure and is at present 86 per cent.

I hesitated considerably before resorting to transfusion in this patient, because at first glance it seemed to be exactly contrary to therapeutic teaching. We are warned not to overburden the heart and circulation already taxed by the resistance offered by the inflamed lung. As a matter of fact, depletion of the circulation by venesection would seem to be a much more rational procedure. However, the child's condition changed remarkably within a few hours after the transfusion and he promptly recovered.

Whether this recovery was due to a direct effect of the transfusion on the pneumonic process I am unable to say. It is, of course, possible that this child might have had a crisis without the transfusion and that we just happened to give the blood at a favorable moment. However, later experiences have taught me that apparently there is a connection between the recovery and the transfusion. I have transfused ten children in the course of pneumonia and have noticed improvement immediately following the procedure in all the cases. I believe that the rationale for this form of treatment is based on the fact that the blood simply supplies substances, which assist in the resistance to infection. It enables the previously anemic child to overcome the pulmonary infection, much as a transfusion assists a sepsis patient of any other kind in the fight for life.

It has happened, as will be observed by a study of the charts, that in a number of cases a critical drop to a permanently normal temperature has followed the transfusion. In other cases, the changes in the child's general condition, the dyspnea, the cyanosis, the mental state and the appetite, have been immediate and striking, though the temperature has come down to normal gradually over a period of several days.

ANEMIA AND PNEUMONIA

The question naturally arises as to whether there is any direct connection between the presence of the anemia and the lack of resistance to pneumonia. The relationship of anemia and pneumonia is only mentioned casually in medical literature.

Thus de la Camp, in Kraus and Brugsch's System of Medicine, says: "As the white blood cells are increased the red cells are diminished." Naegeli, in his book on the blood, states: "The red cells are often somewhat reduced in number; still greater is the reduction

in hemoglobin." The question, however, has not been frankly discussed as to whether there is a real anemia, that is, a real destruction of blood, or whether for some reason the normal amount of blood is not available to the circulation. As long ago as 1895, Bollinger made some very pertinent observations in cases of lobar pneumonia in adult patients coming to necropsy. He pointed out that death might be due to circulatory failure caused by oligemia. He noted that the organs of patients who had died of pneumonia seemed bloodless, and that the affected lung seemed to contain exceedingly large amounts of blood. The weight of the normal lung in males is to the total body weight as 1 : 58; in females as 1 : 66. Pneumonic lungs in half of his cases weighed over 1,000 gm., and in some as high as 1,500 gm. The normal lung contains from 7 to 9 per cent. of the total amount of blood in the body; the pneumonic lung, on the other hand, contains from 30 to 40 per cent., if we consider the whole exudate as derived from the blood. Bollinger says (translated):

> According to my conception, the exudate in croupous pneumonia has the same significance for the whole body, as a recurrent internal hemorrhage occurring under favorable circumstances (fever, infection).

And to quote him further:

> The critical appearance of collapse in croupous pneumonia, and the fatal cardiac insufficiency are caused by the oligemia, which leads to impaired nutrition of the weakened and overtaxed heart muscle.

Bollinger, however, went no further than this. He merely deduced facts from observations on the cadaver, though he suggested that to increase the volume of the circulatory blood, saline infusions might be beneficial.

Quite recently the question has again appeared in the literature, this time in the form of observations on animal experiments. Leake and Brown, in the *Journal of Experimental Medicine* in 1922, report their experiences in a series of dogs in which they had produced experimental pneumonia. During the course of an investigation of experimental pneumonia in dogs, red blood cell counts were made as a routine procedure. The authors thought that there would be a compensatory rise in the number of erythrocytes to counteract the effect of interferences with blood oxidative processes in the lung. They found that quite the opposite was true: in all these animals there was a marked decrease in the red cells as the disease progressed. Forty-six dogs were intratracheally injected with suspensions of organisms (*B. bronchisepticus* and *B. Mucosus capsulatus*), and the resulting lesions were followed by means of the roentgen ray. Twenty cubic centimeters of blood was drawn daily for determinations. If the animal recovered, the tendency to return to the normal count was not pronounced or in proportion to the speed of the recovery. As an example, the authors cite a dog which

before infection showed 6.6 million red cells. Two days afterward, the number dropped to 5.2 million; two days later, when the dog was very sick, there were 4.4 million; and three days later, just before death, there were 3.6 million. The uniformity of the results raised the question as to whether the blood was an actual loss of circulatory red cells or whether the blood was merely diluted. To settle this question, these observers estimated the blood volume, determined the hemoglobin by Palmer's method and used the hematocrit. The blood volume was found to remain constant; the hemoglobin fell in proportion to the number of red cells, and there was a marked increase in the plasma with a corresponding fall in the mass of formed elements. Control animals showed no such changes. These considerations indicated, in Leake and Brown's opinions, an actual loss of erythrocytes in the effective circulation without a compensatory regeneration of blood. They then proceeded to examine the tissues of the dogs histologically, and discovered large numbers of red cells in different stages of degeneration in the capillaries and tissue spaces of the lungs, liver, spleen and intestinal walls. The capillaries in all these organs were gorged with red blood cells. These findings, the authors believe, are enough to account for the absence of sufficient cells in the circulating blood.

From the foregoing findings we are led to believe that a withdrawal of blood cells from the circulation may take place in the course of pneumonic inflammations of the lungs. May not some of the untoward symptoms of the disease be brought about by this very condition; and if so, may not the introduction of fresh blood into the circulation aid the body in ridding itself of the infection?

COMMENT

We have no definite explanation to offer for our results. It is possible that we are dealing with a form of serotherapy, that we are introducing antibodies of some sort which neutralize the toxin of the disease. Or we may be supplying cells to carry such needed oxygen to the tissues, to replace those blood cells which have been withdrawn from the circulation by the diseased process in the lungs and other viscera. Again we may, by increasing the blood volume, in some way affect the heart so as to overcome the cardiac weakness.

Whether or not the transfusion acts in such a specific manner as before indicated must be left an open question, as the evidence as detailed in the foregoing is very slight; yet a perusal of the accompanying case histories will, I think, make it clear that the transfusion is an extremely valuable therapeutic asset. Especially is this true in cases in which there appears to be a prolonged struggle between infection and the child's resistance, and in which new foci, both in the lungs and elsewhere, keep on appearing. In such cases, the addition of the healthy

blood may be the factor which causes the balance to swing toward the side of increased resistance and recovery.

That blood transfusions are of great use in prolonged or in very virulent infections is no new idea, but the fact that pneumonic infections also may be benefited is not generally known.

In infants and young children, pneumonia is decidedly not a contraindication to transfusion. We have seen no case in which the child seemed to be harmed by the procedure. We have transfused in the presence of severe dyspnea and cyanosis without untoward results. We have taken blood pressure readings before and after the transfusion and found practically no change. The fluid introduced is quickly compensated for by vasodilatation, and there are no signs of circulatory embarrassment during or after the procedure.

We employed citrated blood in three cases, and whole blood by the Unger method in the remainder. Except in Case 1, there were no severe reactions.

Whether this form of treatment is applicable only to infants and children I do not know. One must remember that there is a difference in the circulatory efficiency in infants and children as compared with adults, the so-called lability of the circulation in early life, which possibly accounts for the lack of circulatory embarrassment during or after the blood transfusion. I have tried it only in children, all of them, with one exception, under 3 years of age. The youngest child in which it was attempted was aged 4 months (Case 7). This infant (one of twins, as the case report shows) was extremely ill, was markedly rachitic and anemic, and had an ear discharge for three months. The infant's condition was very poor, respirations were 100 per minute, and the pulse was poor in quality. The transfusion was done at 1 p. m., while the temperature was 103.8, the respirations 100 and the pulse rate 168. At 6 p. m. the temperature was 102.2; at 2 a. m., 100.4 and at 10 a. m., 97.8, after which it never went above 98.

SUMMARY

Ten cases of pneumonic infections occurring in anemic infants are described. All of these were treated by means of human blood transfusions. The results show that the addition of the new blood was accompanied not only by improvement in the anemia but in cure of the infection, in some cases in a manner similar to a crisis. Nine patients recovered. One patient suffering from celiac disease with secondary infection, improved considerably for a time but finally died of purulent meningitis.

Blood transfusion is advised as being helpful in the treatment of anemic infants and young children, especially when the anemia is complicated by pneumonia. It is not being urged as treatment for pneu-

monia but as a cure for the anemia, as a result of which the pulmonary infection is apparently checked. Heretofore pneumonia has been considered a contraindication to blood transfusion, but in our experience the opposite is the case, for when a child with severe anemia is stricken with a pulmonary infection, the chances for recovery seem to be greatly increased by the use of transfusion.

CONCLUSION

There is apparently a definite rationale for the employment of blood transfusion, during the course of certain cases of anemia with complicating pneumonia.

For anemic children who contract pneumonia, we possess in blood transfusion a very valuable and potent therapeutic agent. Pneumonia in such cases, should be considered not as a contraindication to the use of transfusion, as heretofore, but as a distinct indication for such treatment, especially as there is no danger involved either during or immediately following the transfusion.

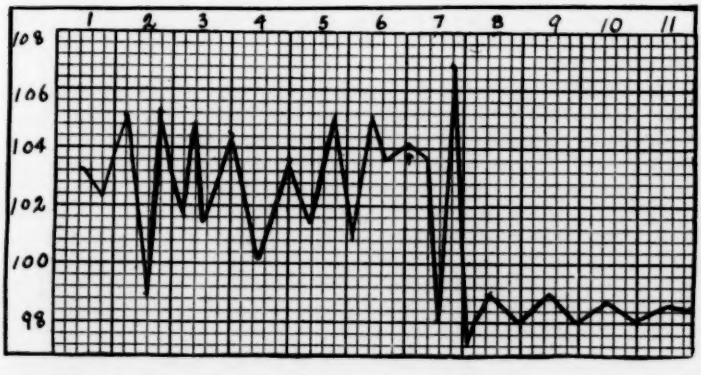

Fig. 1.—Temperature chart of Case 1; arrow points to transfusion on seventh day of illness.

REPORT OF CASES

CASE 1.—S. S., Jr., a boy, was a rachitic child with a long and difficult feeding history. In March 1917, when aged 18 months, he developed severe lobar pneumonia. At this time the weight was 17 pounds 4 ounces, hemoglobin 32 per cent. The chest showed signs of pulmonary consolidation of the right middle and lower lobes. On the seventh day of illness the child appeared moribund. The temperature was from 104 to 105. The pulse was up to 192. Respiration 84. Marked abdominal distention and cyanosis were present.

As a last resource, a transfusion of citrated blood obtained from the patient's mother was given. Immediately after the transfusion the temperature dropped to 99, to rise within an hour to 106.8, with chill. After this there was an immediate drop to 99.2, followed by continued normal temperature and rapid recovery.

Pulmonary resolution began two days later.

Following the transfusion, the hemoglobin rose to 70 per cent. where it remained.

This child has been under observation to date and has had no recurrence of the pulmonary condition, nor has the anemia returned.

CASE 2.—M. D., aged 2 years, was admitted to Mount Sinai Hospital March 3, 1923, with a history of cough for two weeks and fever for five days. The child was acutely ill, dyspneic and cyanotic, with signs of bronchial pneumonia at both bases. Two days later the temperature rose to 106.8, and definite signs of consolidation appeared in the right upper lobe. Physical signs remained unchanged, but the child became more pale and the general condition grew worse. March 13, the hemoglobin had fallen to 39 per cent. The red blood cells were 3,210,000; white blood cells 15,000. As a last resort a transfusion of 175

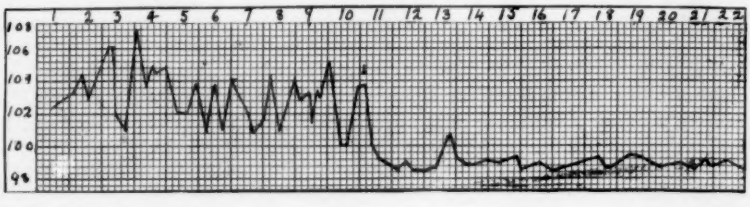

Fig. 2.—Temperature chart of Case 2; arrow points to transfusion on seventeenth day of illness, followed by critical drop to normal temperature.

c c. of human blood was given by the Unger method. Great improvement was noted. The temperature reached normal after twelve hours. Hemoglobin gradually increased, reaching 80 per cent. when the child was discharged cured, one month after admission.

CASE 3.—B. T., a girl, aged 2 years, was admitted to Mount Sinai Hospital, March 1, 1923, with a history of fever and cough for three days. She showed signs of disseminated bronchopneumonia over both lower lobes and in the right axilla. For three weeks the child ran a septic temperature, new foci of pneumonia appearing from time to time. Hemoglobin test (taken after two weeks of illness) showed 48 per cent. On the twenty-third day of illness, while the child's condition was grave, with dyspnea, cyanosis and pallor present, 400

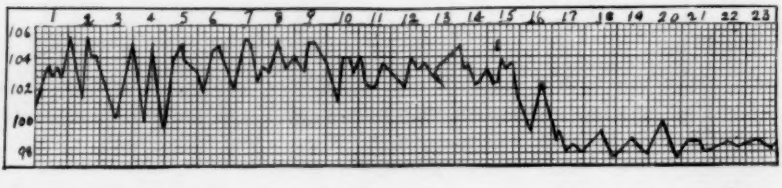

Fig. 3.—Temperature chart of Case 3; arrow points to transfusion on twenty-third day of illness, followed in two days by normal temperature.

c.c. of blood was given by the Unger method. The improvement was remarkable; within twenty-four hours the fever dropped to normal, the child sat up in bed, took food eagerly, although the physical signs at this time remained unchanged. The hemoglobin rose at once to 85 per cent., the temperature remained normal and the child made an uninterrupted recovery.

CASE 4.—S. M., a girl, aged 2 years, with a previous history of many infections, was admitted to Mount Sinai Pediatric Service, June 2, 1923, suffering from nasopharyngitis and bronchopneumonia. The pneumonia spread steadily, so that on June 8, six days after admission to the hospital, there were signs of involvement of all the lobes in both lungs. Leukocytes were 26,400, 80 per cent. polymorphonuclear neutrophils, 20 per cent. lymphocytes. The hemoglobin

(Sahli) was 47 per cent. On account of the desperate condition of the child (marked distention, cyanosis, poor pulse, great prostration) 80 c.c. of the mother's blood was given by the Unger method and, there being some difficulty with the apparatus, 175 c.c. of citrated blood. Following this, the general condition seemed improved, the child took her food a little better and seemed brighter. The lung signs remained unchanged. June 9, the hemoglobin was 51 per cent.; June 12, 55 per cent. June 12, a paracentesis of both ears was necessary. Two days later the child's condition was again desperate, and on account of the temporary improvement following the first transfusion, it was decided to transfuse

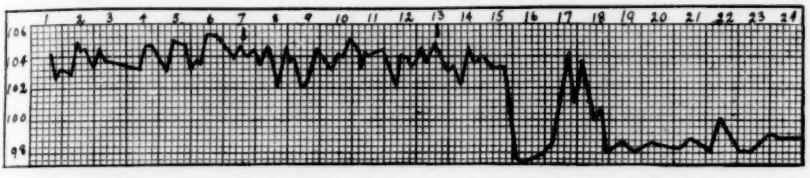

Fig. 4.—Temperature chart of Case 4. Arrow points to transfusion on the seventh day after admission, followed by improvement in symptoms but continued high fever. Second transfusion given six days later was followed after forty-eight hours by critical drop to normal temperature.

again. June 14, the hemoglobin had fallen to 48 per cent., and 160 c.c. of citrated blood was transfused into the median arm vein. Forty-eight hours later the temperature fell to 98, signs of pulmonary resolution appeared, and the child made a perfect recovery.

CASE 5.—M. S., a boy, aged 9 months, who had been ill with some undiagnosed febrile condition for three months prior to admission, was admitted to Mount Sinai Hospital, May 10, 1923, with suggestive signs at the left base which gradually developed into distinct lobar pneumonia of the entire left lung. The

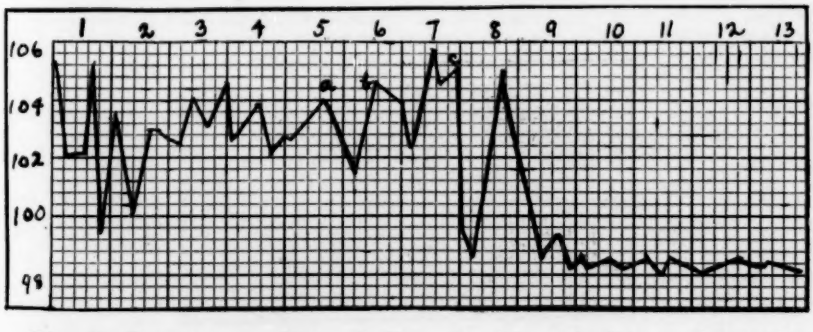

Fig. 5.—Temperature chart of Case 5; (*a*) and (*b*) myringotomies; (*c*) transfusion.

child became toxic, looked very ill, the hemoglobin dropped from 72 to 55 per cent. and bilateral purulent otitis media developed (myringotomy). Nine days after admission (on thirtieth day of illness) 140 c.c. of blood was transfused by the Unger method. The temperature fell to normal, rose again the following day, and fell again to normal permanently. Gradual resolution of the lung followed.

CASE 6.—S. S., a boy, aged 1 year, was admitted to Mount Sinai Hospital with a temperature of 104, and signs of right sided bronchial pneumonia and bilateral otitis media.

The leukocyte count was 16,600, polymorphonuclear 63 per cent.; hemoglobin 56 per cent. Both ear drums were incised. On the sixth day after admission (seventh day after illness), the temperature dropped by crisis to normal. At this time the hemoglobin was 48 per cent.

For six days the temperature remained normal and the hemoglobin rose to 53 per cent. For five days the child ran irregular temperatures up to 104.2. The leukocyte count rose to 41,400, with 75 per cent. polymorphonuclear cells.

Signs of pneumonia again appeared in the right upper lobe, and the child appeared to be very sick. The hemoglobin had again fallen to 48 per cent. and

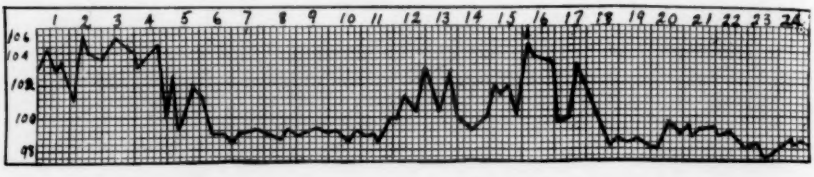

Fig. 6.—Temperature chart of Case 6. Recurrent bronchial pneumonia; arrow points to transfusion on sixteenth day of illness.

the red blood cells were 2,900,000. A transfusion of 309 c.c. of citrated blood was given, when the temperature was 104.4. Following this, the temperature fell by crisis to normal, rose the following day to 103 and fell to normal where it remained. Hemoglobin rose to 72 per cent.; red cells, 3,640,000. The blood pressure which before the transfusion had been 112 systolic, 82 diastolic, fell to 100 systolic, and 68 diastolic, and twenty-four hours later returned to 110 systolic, 82 diastolic.

The child made an uneventful recovery.

CASE 7.—L. L., a boy, aged 5 months, one of premature twins, was seen on Dec. 5, 1923. Since his fifth week the infant had had many attacks of purulent otitis media and had shown signs of rickets and anemia. December 2, the baby became sick with bilateral otitis media, followed the next day by pneumonia of

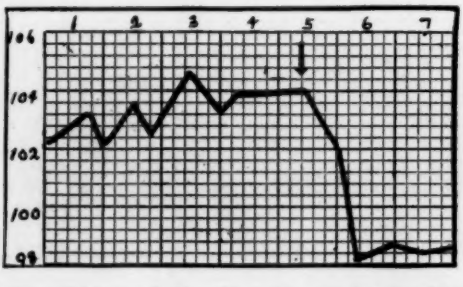

Fig. 7.—Temperature chart of Case 7; twin, aged 5 months, with hemoglobin of 50 per cent.; arrow points to transfusion when the infant was almost moribund.

the right upper lobe. The infant appeared extremely ill, the respirations reached 100 per minute, the pulse 160 which was very feeble. The abdomen was markedly distended and the lips and finger tips were cyanotic. Hemoglobin was 50 per cent. Red blood cells 2,800,000, white blood cells 9,200. In view of the almost hopeless appearance of the child a transfusion of 200 c.c. of the father's blood was given. Within twelve hours the temperature was normal, the cyanosis had disappeared and the baby made a rapid recovery.

December 20, the hemoglobin was 91 per cent. Red blood cells 4,800,000, white blood cells 8,000.

CASE 8.—D. P., a boy, aged 11 months, was admitted Sept. 20, 1924. The child had been born prematurely at seven months and was one of twins. At the age of 3 months he had an attack of bronchopneumonia. He never throve well. For two days previous to admission the child vomited, had loose stools and fever. Examination showed a marantic baby, weighing 8 pounds 7 ounces (3,827 gm.), very pale, dehydrated and rachitic. At the right base there was distinct dulness and fine râles. The temperature rose to 105. After twenty-four hours in the hospital his weight had fallen to 8 pounds 1 ounce and the child

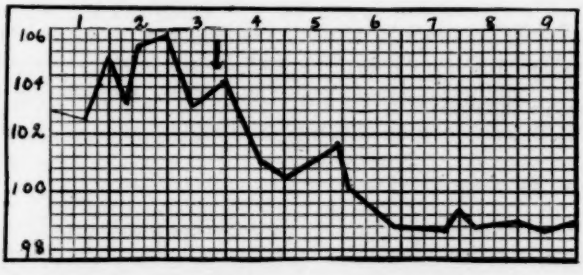

Fig. 8.—Temperature chart of Case 8; a twin, aged 11 months; arrow points to transfusion when apparently the infant was hopelessly ill.

appeared hopelessly ill. White cells, 14,600, polymorphonuclears 66 per cent., lymphocytes 34, hemoglobin 60 per cent. Red cells 3,400,000 (probably due to dehydration. One hundred and seventy-five cubic centimeters of human blood was given into the longitudinal sinus with immediate improvement. Five days later the hemoglobin was 78 per cent. In eleven days the patient gained 17 ounces and made an uneventful recovery.

CASE 9.—F. C., a girl, aged 18 months, was admitted to Mount Sinai Hospital, July, 1924, where she was under treatment for celiac disease. Her weight on admission was 13 pounds (5,896 gm.). The blood examination was normal

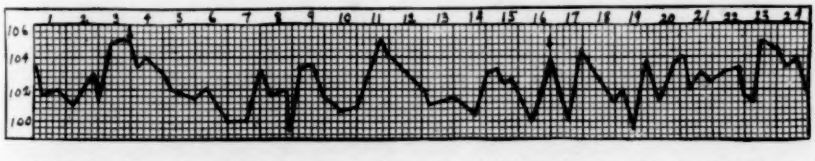

Fig. 9.—Temperature chart of Case 9. Celiac disease in a child, aged 18 months, with secondary bronchopneumonia. Temporary benefit after two transfusions into median basilic vein (shown by arrow); death from purulent meningitis.

(hemoglobin 80 per cent.). Under treatment she throve well, so that on August 28 she weighed 16 pounds 8 ounces (7,490 gm.). At this time she contracted an infection, characterized by pharyngitis and bronchopneumonia. In ten days the hemoglobin fell from 75 per cent. to 47 per cent. She appeared extremely ill, ran a high fever and was greatly prostrated. On August 30, the child received 150 c.c. of human blood intravenously. She reacted very well and on the day following the transfusion was seen walking about in her crib. Hemoglobin rose to 57 per cent. but the lung signs remained unchanged. September 13, on account of continuance of septic temperature, she was given 150 c.c. of blood intra-

peritoneally. There was no unfavorable reaction. The blood cultures were repeatedly negative, the urine normal. September 20 the patient had a general convulsion with signs of meningitis. The spinal fluid was purulent, culture showing streptococci. September 24 the child died.

Summary.—An infant, aged 18 months, suffering from celiac disease, contracted an infection which lasted for four weeks. This caused a rapid fall in hemoglobin, from 75 to 47 per cent. In spite of the presence of bronchopneumonia, blood transfusion was given which resulted in distinct though only temporary improvement.

CASE 10.—C. G., a boy, aged 10 months, was admitted to hospital Aug. 16, 1924, with a history of otitis, coryza, cough and fever for two weeks. Examination showed a well nourished, pale baby, coughing and both ears discharging. There was distinct dulness in the right axilla and general coarse râles.

Course.—August 19, the temperature was down, the lungs were clear and the ears stopped discharging. The patient was hoarse. Hemoglobin, 57 per cent. Red blood count, 3,200,000.

August 21, both drums were bulging. Paracentesis was done. The lungs were clear.

August 22, follicular tonsillar exudate.

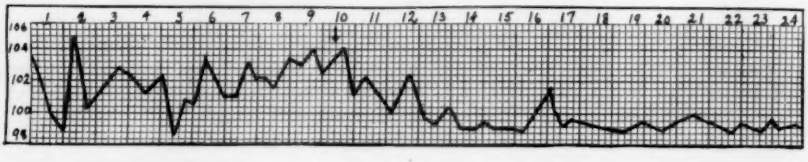

Fig. 10.—Temperature chart of Case 10; a child, aged 10 months, with tonsillitis, double otitis and secondary bronchopneumonia. Arrow points to transfusion when the child was apparently moribund.

August 24, white blood count 16,000, polymorphonuclears 78, lymphocytes 22.

August 25, hemoglobin, 58 per cent.

August 25, the left base gave moist râles (roentgen ray showed pneumonia at the left base).

August 27, the left base showed faint bronchial breathing.

August 29, the pneumonic process extended upward to the angle of the scapula.

September 2, the general condition very poor, the temperature was up to 104. The pneumonic process had involved the entire left side. Hemoglobin, 55 per cent.

September 3, 220 c.c. of blood was given into the sinus. Immediately there was a favorable reaction. The child appeared to be moribund before the transfusion.

September 4, the hemoglobin was 60 per cent. Transfusion helped the child, and recovery proceeded rapidly after this.

September 21, the hemoglobin was 64 per cent.

The weight on admission was 17 pounds and fell to 15 pounds, 4 ounces, on the day of transfusion, and rose gradually in two weeks to 17 pounds, 9 ounces.

57 West Ninety First Street.

THE TREATMENT OF DIABETES IN CHILDREN *

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A survey of the literature on diabetes reveals that scant attention has been paid to juvenile diabetes, as such. In the past, this has been due in part to the reputed rarity of the condition and in part to the notoriously bad prognosis warranted in most cases. This latter factor has caused many authorities, including Von Noorden, to consider downward progress as so inevitable that the necessary harsh restrictions of treatment were unjustifiable. Indeed, it was not until 1914, when Allen [1] elaborated his system of treatment that a happier outcome was shown to be possible.

The indications for treatment in children are the same as in adults, only more urgent, because of the acute nature of the disease in the young. Functional rest for the pancreas, to allow of all possible recovery, as provided by suitable dietetic measures, or by these plus adequate insulin is the essential part of treatment. The best criterion that such rest is being given is afforded by the maintenance of a normal blood sugar and the absence of glycosuria. As Allen [2] has shown, overstimulation of the pancreas is caused by hyperglycemia, and rapid degeneration of the islet cells occurs. The progress of the disease in its presence is steadily downward.

Another problem insulin has created in the treatment of juvenile diabetes, by making its consideration possible, is the optimum nutritional state in which to maintain the diabetic child. Joslin [3] and others have pointed out the dangers of obesity in diabetes, but data are wanting that indicate any advantage in undernutrition in the child whose blood sugar is kept under control by suitable dietetic measures plus adequate insulin. The healthy, well nourished, but not obese children who attend our diabetic clinic now offer a striking contrast to the dwarfed, undernourished patients of former times. The fact that the tolerance to

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* From the Wards of the Hospital for Sick Children, Toronto, and the Subdepartment of Pediatrics, University of Toronto.

* This work was made possible by the gift of $10,000 from John D. Rockefeller, Jr.

1. Allen, F. M.: Monographs of the Rockefeller Institute for Medical Research, No. 11, 1919.

2. Allen, F. M.: J. Metabol. Res. **1**:75-88 (Jan.) 1922.

3. Joslin, E. P.: Treatment of Diabetes Mellitus, Washington, Carnegie Institute of Washington, 1923.

carbohydrate has increased in practically all of them, while in a normal nutritional state, is strong evidence that normal weight is not contraindicated.

INSULIN

Insulin, so far as is known at present, is not a cure for diabetes. It is, however, invaluable used in conjunction with dietetic measures in severe or complicated cases and acts as a specific in the treatment of acidosis and coma. Dietetic measures alone prove sufficient in a large proportion of adult patients. Graham [4] has estimated that 75 per cent. of the adult cases can be controlled by this means alone. With children it would be nearer the truth to state the reverse. This large majority could not be successfully treated without insulin, as the following figures obtained from the food tolerance of the last fifty cases treated at the Hospital for Sick Children, would indicate: Twenty-eight cases, 56 per cent., were unable to take their basal requirements without glycosuria; seventeen cases, 34 per cent., were unable to take sufficient food to grow on; five cases, 10 per cent., could take adequate nourishment.

The results obtained with the best treatment of diabetes in children, prior to the discovery of insulin, furnish abundant evidence of its necessity in their treatment. Under favorable conditions they lived from two to six years, dwarfed in stature and semi-invalid. The larger proportion fared worse. Those who remained faithful died from inanition rendered inevitable by such low caloric diets as their tolerance permitted. Many of these patients were not receiving their basal requirements, as Talbot [5] has shown. Others succumbed to coma brought on by dietary indiscretion, neither they nor their parents being willing to adhere to such harsh restrictions as were found necessary.

How will the use of insulin effect the results of treatment? The two years that have elapsed since the extract has been available has been too short a time to determine its possibilities. Thirty-one of the thirty-five patients treated for a year or more have shown a marked and progressive improvement in tolerance. In two patients the tolerance has been more than doubled in a year, in one it has been more than trebled in that time. The dose of insulin in every instance, where the child remained faithful to diet, has had to be reduced and this in spite of their increasing weight. One of the patients in which the tolerance has been doubled has also increased his weight 100 per cent. Of the two patients that have progressed downward, one has been grossly unfaithful and has had coma resulting from dietary excesses. The second child demonstrates the danger of ignoring knowledge gained hitherto, regarding the necessity of control of glycosuria. Her family physician is one of those who

4. Graham, D.: University of Toronto M. Bull. April, 1923.
5. Talbot, F. B.: Personal communication.

regard the presence of small amounts of sugar in the urine as a justifiable safeguard against hypoglycemic reactions. Her general condition is excellent but as Chart 1 shows, the disease, instead of being checked has actually progressed as indicated by her increasingly lower tolerance. The diet is the same throughout the period covered by this chart.

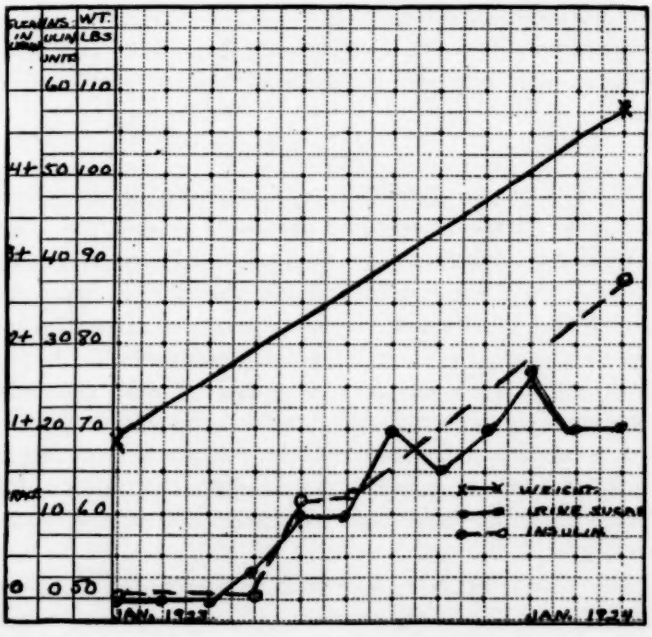

Chart 1.—Progress of the diabetes. Instead of being checked, the disease has actually progressed.

STANDARDIZATION

The potency of each lot of insulin is determined by means of physiologic assay. A unit may be defined as one-third of the amount necessary to reduce the blood sugar of a rabbit, weighing 2 kg., which has fasted for twenty-four hours, to 0.045 per cent. in three hours. It is impossible to give any accurate definition of the unit of insulin measured in grams of carbohydrate, which it renders utilizable to a person, as susceptibility to its action varies widely. Most observers estimate the glucose power of a unit of insulin as approximately from 1 to 2 gm. of glucose. The crudity of such computations of the amount of glucose rendered available by a unit of insulin is evident when one considers the inaccurate methods determining the amount of foodstuff being burned at any one time. Allen [6] states that increased body weight increases the

6. Allen, F. M.: J. Metabol. Res. **1**:5 (Jan.) 1922.

need for insulin independent of the caloric intake. If this is true, the true increase in tolerance in the children we treated has been greater than was apparent. All of them were gaining weight, sometimes rapidly, and yet the number of units of insulin needed to keep them sugar free steadily decreased. It is of course, possible that increased weight, largely of adipose tissues, in an adult, may increase the insulin need more than growth of the bone and muscle tissues which constitutes a large proportion of the increased weight in children. Experience and skill in the administration of insulin permit the use of smaller doses to accomplish like results.

DOSAGE

The difficulty of giving any accurate estimation of the power of the unit of insulin renders the question of dosage an individual one. The desired result is to make and keep the patient aglycosuric and his blood sugar normal. When it has been shown that this is impossible on a greatly restricted diet such as his basal requirements or less, insulin is indicated. The preliminary determination of the blood sugar will render such mistakes as treating renal glycosuria with insulin and thus causing a reaction unlikely, and will give a rough indication of the required amount. When this preliminary precaution is taken, doses of from three to five units twice a day may be given with safety at the start, and the amount increased, or decreased, as the effect produced suggests.

The time of administration is of much importance in the effectiveness of any dose given. Too little attention to this factor may result in the same patient having symptoms of a reaction of more or less severity during the day and yet having sugar in the twenty-four hour specimen of urine. This can be avoided by examining two hourly specimens of urine and regulating the dose by the findings. Patients in which the total requirement is less than 10 units usually do well with a single dose, given from fifteen to twenty minutes before breakfast. Woodyatt [7] and Wilder [8] and his associates recommend the use of single doses half an hour before breakfast in the majority of cases. We have not found such a method satisfactory when the dose exceeded the 10 units mentioned, as hyperglycemia, with or without glycosuria occurred some time within the twenty-four hours. Further, as Campbell and Fletcher [9] have pointed out, with such a method acetonuria was found during the later

7. Woodyatt, R. T.: Objects and Method of Diet in Adjustment in Diabetes, Arch. Int. Med. **28**:125 (Aug.) 1921.

8. Wilder, R. M., and Boothby, Barbarka, Kitchen and Adams: J. Metabol. Res. **2**:708, 1922.

9. Campbell, W. R., and Fletcher, A. A.: J. Metabol. Res. **2**:637, 1922.

part of the day. In patients receiving from 10 to 30 units daily, it may as a rule be given in two doses before the breakfast and evening meal, if these are spaced twelve hours apart and the noon meal is made somewhat lighter in food value. Satisfactory division of the dose must be determined by the examination of the two hour urine specimens, and in those rare instances in which sufficient of the total cannot be given before breakfast to produce effects lasting until evening, three doses must be given. When more than 30 units daily is needed, it is advisable to distribute it in three doses of about equal values before meals.

REACTIONS

When more insulin than is necessary is given to reduce the blood sugar to normal, a train of symptoms known as a hypoglycemic reaction ensues. The usual symptoms in children are abnormal epigastric sensations, hunger or actual pain, and emotional disturbances. The latter are more commonly noticed in the younger children. They consist chiefly of crying spells or of periods of unreasonable irritability coming on suddenly. The older children more often complain of hunger pains alone or associated with dizziness. The pulse is rapid and perspiration increased. Strabismus is frequent. If untreated, coma and later convulsions occur. The proneness of children to react to many and varied pathologic stimuli with convulsions probably accounts for the greater frequency of this type of reaction in the young. We have seen convulsions in four patients with the following percentages of blood sugar, 0.038, 0.040, 0.059 and one unknown. The lowest blood sugar, 0.038 per cent., was found in a boy, aged 11, after the convulsions had been succeeded by deep coma in which none of the superficial nor deep reflexes could be obtained, and the boy appeared to be dead. The response to intravenous glucose in this patient was miraculous. He sat up and was interested in his surroundings after receiving only 100 c.c. of 5 per cent. glucose, and was normal in every way within half an hour of the injection of 300 c.c.

Ill-defined symptoms, such as vague uneasiness or slight dizziness, usually occur when the blood sugar is between 0.07 and 0.08 per cent., and the more pronounced epigastric or emotional ones when it is between 0.06 and 0.07 per cent. There is, however, considerable variation in the level of blood sugar at which symptoms occur, namely, one child with a blood sugar of 0.04 per cent. exhibited only the indefinite symptoms usually seen at higher levels, whereas another had profuse perspiration and tachycardia with a blood sugar of 0.096 per cent.

TREATMENT

The low level of the blood sugar at which reactions occur, immediately suggests giving carbohydrate as the proper therapeutic measure.

Noble and MacLeod [10] have shown that any form of carbohydrate readily convertible into glucose is effective. From 20 to 25 gm. of carbohydrate is usually the maximum requirement even in severe reactions. This may be given by mouth in the form of orange juice, or glucose solution if the patient is conscious. The injection of 10 mimims of 1 : 1,000 solution of epinephrin increases the blood sugar rapidly in all but those whose glycogan storage is very low, and usually renders the comatose patient able to take carbohydrate by mouth. Should it fail to do so or the reaction be so severe that deep coma or convulsions are present, glucose must be given intravenously.

The general increase in the tolerance of cases under control, mentioned before, has resulted in the production of mild reactions in most of our cases. After from 6 to 8 weeks on a diet with the dose of insulin needed to keep the blood sugar normal, the child begins to have mild reactions almost daily, indicating probably an increase in the insulin production of his own pancreas and consequent decreased need of the artificial extract.

DIET

The importance of dietetic measures in the control of diabetes is now universally recognized. Insulin employed in conjunction with suitable dietetic treatment renders unnecessary the harsh, often intolerable, restrictions frequently found necessary in the past. It in no way minimizes the vital importance of dietetic treatment. Due regard must be given to the food intake if the optimum dose of insulin is to be given, otherwise hyperglycemia will alternate and the progress of the disease will be steadily downward. Further, as Joslin [11] has pointed out, carelessness with the diet, because of insulin, will increase the incidence of coma and consequently the mortality.

Numerous dietaries of diverse compositions have been advised. Successful treatment, in certain cases at least, has been achieved with many of them. The majority have aimed at the restriction of carbohydrate within the patients' tolerance. Failure to produce results was often explainable by the neglect to estimate the large amounts of carbohydrate that might be derived from foods other than starches and sugars, notably the protein in computing the carbohydrate intake. During the last ten years, as a result of Allen's work, undernutrition has come to be regarded as a valuable aid in checking the disease. It was a necessary accompaniment of a diet rigid enough to maintain the blood sugar at a normal level in many cases. Opportunity of judging whether or not a normal nutritional state was in itself a depressant of pancreatic function when the blood sugar was normal did not often arise. Insulin has

10. Noble, E. C., and MacLeod, J. J. R.: Am. J. Physiol. **64**:547 (May) 1923.
11. Joslin, E. P.: Treatment of Diabetes Mellitus, 1923.

made it possible to keep the blood sugar normal regardless of the weight. Allen [12] still urges moderate undernutrition, and states that the dose of insulin needed by an individual varies with the weight. We have observed no increasing need of insulin with increased weight, if the patient was constantly aglycosuric and the blood sugar normal. The case shown in Chart 2 demonstrates a consistently decreasing need of insulin with gain in weight. This child was no exception to the general rule in this regard, but his tolerance has increased a little more rapidly.

No contraindication to the maintenance of the diabetic child's nutrition at the standard normal level has been encountered in our series of cases. The curves in Chart 3 were recently published by Talbot,[13] and

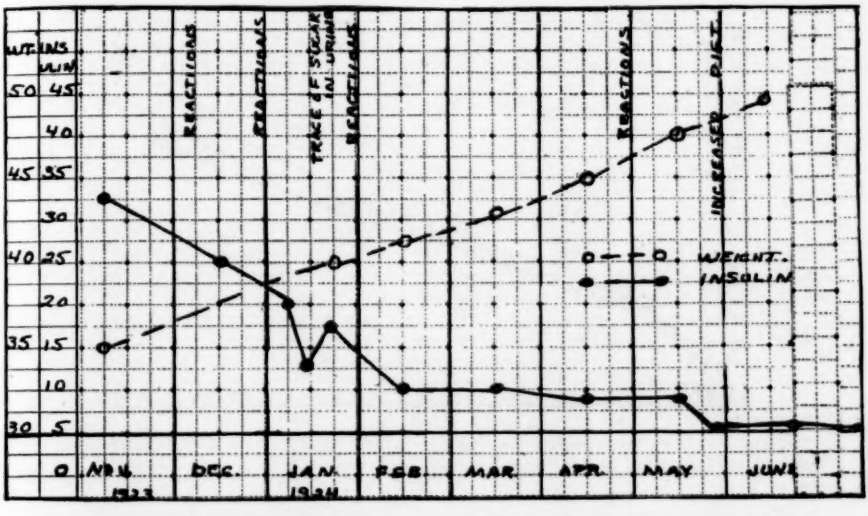

Chart 2.—This chart demonstrates a consistently decreasing need of insulin.

were obtained from measurements of the average American child. In no case do they represent overnutrition. Talbot [14] questions whether such low figures represent the physiologically desirable weight, as when working with private schoolchildren living under ideal conditions he found the average weight and height considerably higher. The large numbers of healthy schoolchildren, who compared to these figures are overweight and yet do not appear obese, would suggest that these figures are minimal in perfect health. Biometric measurements of private schoolchildren, such as those obtained by Holt, are appreciably higher than Talbot's figures.

12. Allen, F. M.: J. Metabol. Res. **2**:803, 1922.
13. Talbot, F. M.: Studies in Growth, Am. J. Dis. Child. **27**:541 (June) 1924.
14. Benedict and Talbot: Pub. 302, Carnegie Inst.

Maintenance of a normal nutritional state has materially lessened the susceptibility to infections in diabetic children. The proneness of the undernourished diabetic child to infection and the depressant effect of the latter on pancreatic function is too well recognized to need comment.

Another more valuable feature of the larger diets has been the decrease in neglect to treatment with them. This is a factor of no little value in treating diabetes, particularly in the young. Only two cases of gross neglect have occurred in thirty-eight children, varying from 2 to 14 in age. Temptation may have proved too strong in isolated instances in the other children, but not often enough to affect materially the treatment.

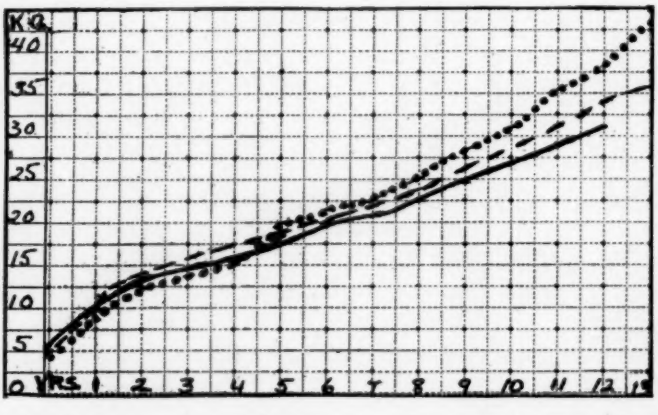

Chart 3.—Normal weight of children according to Holt (dotted line, boys), Talbot (broken line, boys; straight line, girls).

The clinching argument in favor of such adequate diets is the child himself. As long as he is faithful to his diet and receiving adequate insulin, he is to all intents and purposes a normal, healthy child, partaking of all the activities of one. Place such a child against the dwarfed semi-invalid child, who is kept in a state of chronic undernutrition, and the advantages of the former are strikingly apparent.

CALORIC REQUIREMENTS

The energy need of a diabetic child, not markedly undernourished and with his disease under control, may be assumed, at least until proved otherwise, to be the same as a normal child of similar age and nutrition. We have used weight rather than body surface as the unit of measurement. Such a unit is not only simpler clinically but probably just as accurate, as Benedict and Talbot [15] were able to show no greater con-

15. Benedict and Talbot: Pub. 302, Carnegie Inst.

sistency of results in basal metabolism determinations using the surface area than when using weight.

Table 1 gives the estimated caloric requirements of the growing child per kilogram of body weight, according to different authors. These values were obtained chiefly by studying the diets of large numbers of healthy children, and computing their caloric intake. Those of Benedict and Talbot [16] are twice the normal basal metabolism per kilogram per age, determined by these authorities and suggested as a satisfactory method of determining the total caloric need.

TABLE 1.—*The Estimated Caloric Requirements of the Growing Child, According to Different Authors*

Age	Holt: Am. J. Dis. Child. 21:1, 1921	Gillet: N. Y. Assn. for Improvement of Conditions of the Poor, 1917	Benedict and Talbot: Am. J. Dis. Child. 27:541, 1924 2 × Basal	Camerer: Stoffwechael des Kindes, 1906
1	100	105	104	89
	101	105	104	
2	93	90	102	..
	94	93	104	
3	88	83	104	..
	87	83	94	
4	84	79	94	75
	82	79	88	
5	80	77	88	84
	78	73	84	
6	80	75	78.6	Rapid decline from this on
	76	71	80	
7	80	73	84	..
	76	69	76	
8	80	71	80	..
	76	66	76	
9	80	68	76	..
	76	64	74	
10	80	67	74	..
	75	62	72	..
11	80	68	70	..
	80	59	70	
12	80	69	68	..
13	80	62	65	..
	79	51	68	
14	80	54	62	..
	74	48	66	

Chart 4 represents an effort on our part to determine the minimal caloric intake necessary for gain in weight. The requirements of normal children (as given by Holt) and their basal need are added for comparison. The scattered cross marks indicate the individual figures obtained. These vary so widely with the weight of the child at the time of the determination that little information could be obtained from them. Fairly close agreement between the figures obtained is noted, however, when the total calories producing gain are divided by the expected weight for the age. The middle curve on the chart is that obtained

16. Benedict and Talbot: Pub. 302, Carnegie Inst.

when these data are plotted. The general trend of the curve, it will be noted, resembles more closely that of the basal requirements than it does Holt's. Further, it would indicate that about 10 calories per kilogram less than Holt gives would be adequate. It must be remembered, however, that Holt's figures represent the energy intake of children of unrestricted activity, while those from which our figures were obtained were hospital patients who were more or less limited in this respect. The enormous increase needed to meet the exercise requirements of the very active healthy child are given by Lusk [17] to represent such needs under varying degrees of activity, and frequently represent twice the energy requirements of the child when quiet.

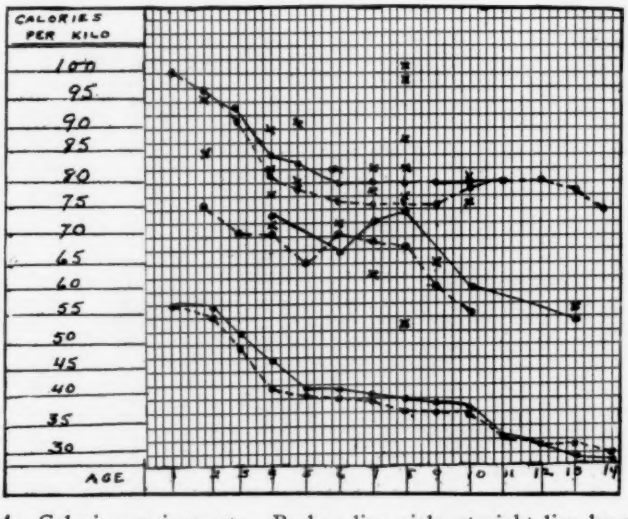

Chart 4.—Caloric requirements. Broken line girls, straight line boys. Upper curve, Holt's figures for requirements of normal children. Lower curve, Talbot's requirements for basal metabolism.

In view of the foregoing observations we have felt that the use of diets computed on the basis of the requirements as estimated by Holt were justifiable. Further, rather than establishing a separate scale of values for the undernourished or overweight child, the caloric requirements have been estimated on the expected weight for the age. By this method those in need of extra food have received it, and dangers of exceeding the requirements per kilogram are automatically checked as the child approaches his normal weight. No child has become obese on diets computed in this way. The few who are overweight for their age are also overheight, so have no excess of adipose tissue. No unfavorable effects on the course of the disease have been noted by keeping the child in good nutritional state.

17. Lusk, Graham: The Fundamental Requirements of Energy for Proper Nutrition, J. A. M. A. **70**:821 (March 23) 1918.

PROTEIN

Recognition at once of the obvious disadvantages of excessive protein in the diabetic patient's diet and the less apparent lethal effects of long continued loss of body nitrogen, has resulted in studies of the minimal nitrogen intake necessary in the adult. Maintenance of nitrogen equilibrium has been regarded as evidence of sufficient intake. The experiments of Hindhede,[18] Chittenden [19] and others have shown that nitrogen balance in adults may be maintained on two-thirds gram of protein per kilogram of body weight, provided their caloric requirements are given. Marsh, Newburgh and Holly,[20] and others, have shown that these laws apply to diabetic patients if their caloric requirements can be satisfied. Protein sufficient to maintain nitrogen balance in children is inadequate if normal growth is to occur.

The amount of protein needed by normal children for growth has never been computed. Statistical studies have been made by numerous authorities of the protein intake of normal children from their diets, and their total requirements estimated from the figures obtained in this way. Such values as given by Holt,[21] Gillet and Gephart [22] vary from about 4 gm. per kilogram daily in infancy and early childhood, down to about 2 in adolescence.

The relatively large amounts of protein ingested by these children makes one hesitate to accept them as the minimal requirements for normal growth. An endeavor was therefore made to determine the protein required (1) to produce nitrogen equilibrium, and (2) to produce a positive nitrogen balance. The usual methods for making such determinations by balancing the nitrogen intake against that excreted were used. In every instance the child was placed on an adequate caloric diet for three or four days before its metabolism was investigated. The food was accurately weighed, and the protein value calculated from Atwater and Bryant's [23] food tables. The nitrogen equals the protein divided by 6.25. Any food not eaten was weighed again and the necessary deductions from the intake made. The nitrogen of the urine and stools was determined by the Kjeldal method.

Chart 5 was drawn when the results obtained in our experiments were computed as protein per kilogram of expected weight. The advan-

18. Hindhede, M.: Skand. Arch. Physiol. **30**:97, 1913; ibid, **31**:259, 1914.
19. Chittenden, R. H.: Nutrition of Man, 1907.
20. Marsh, P. L.; Newburgh, L. H., and Holly, L. E.: The Nitrogen Requirement for Maintenance in Diabetes Mellitus, Arch. Int. Med. **29**:97 (Jan.) 1922.
21. Holt, L. E., and Fales, H. L.: The Food Requirements of Children, Am. J. Dis. Child. **22**:371 (Oct.) 1921.
22. Gephart, F. C.: Bost. M. & S. J. **176**:17 (Jan. 4) 1917.
23. Atwater and Bryant: Bull. 28, U. S. Dept. Agric., 1906.

tage of this method is evident, when one notes the dispersion of the crosses indicating the values obtained calculated to the actual weight of the child.

The lowest intake at any age at which nitrogen equilibrium occurred was 1.25 gm. per kilogram of body weight. This was in a boy, aged 13, barely 10 per cent. below weight and receiving sufficient calories. With an intake of 1 gm. per kilogram, this child had a negative balance. Children more than 10 per cent. underweight required relatively more protein.

These figures must be regarded as the irreducible minimum. No allowance is made for growth, and wear and tear is at a low level as

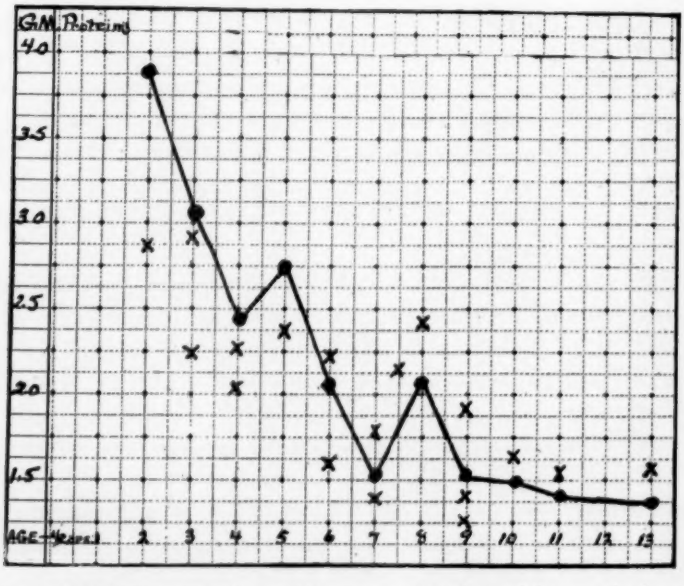

Chart 5.—Minimum protein per kilogram of body weight required to maintain nitrogenous equilibrium.

the child was confined to bed during the metabolism experiment. To allow for growth, there must be retention. Accurate determinations of the amount which should be retained as a growth quota are not available. It is, however, generally believed that a retention of 10 per cent. of the intake will prove adequate. Tables 2 and 3 show the intake of protein per kilogram of body weight needed to insure this retention when the caloric requirements are satisfied.

Determinations of the nitrogen retention when the protein intake was according to estimated requirements (Holt's [21]) are shown in Table 3.

TABLE 2.—*Intake of Protein Per Kilogram of Body Weight*

Age	Sex*	Calories per Kilogram	Protein per Kilogram	Nitrogen		Balance	Nutrition % + or − Standard for Age
				Intake	Output		
2	♀	82.0	3.10	7.200	6.381	+0.818	+12.0
4	♀	87.5	2.20	4.800	2.407	+1.393	−14.0
5	♀	111.0	3.70	9.600	7.139	+2.500	−10.8
6	♂	65.8	2.85	9.600	7.120	+2.480	− 3.0
7	♂	95.6	3.30	7.200	5.706	+1.494	−41.0
8	♀	70.3	1.69	6.400	5.593	+0.807	− 1.6
10	♂	81.7	2.60	11.200	8.923	+2.270	0.0
	♀	81.5	2.58	10.400	7.101	+3.299	−14.0
11	♀	67.5	2.50	12.000	9.525	+2.425	− 8.0
13	♀	57.0	1.59	9.600	7.489	+2.100	− 7.4

* In this column, ♀ indicates female; ♂, male.

TABLE 3.—*Determinations of the Nitrogen Retention*

Age	Sex*	Diet				Protein per Kilogram	Nitrogen			Per Cent. Over or Under Standard Weight
		Fat	Carbohydrate	Protein	Calories		Food	Excreted	Balance	
2	♀	110	50	45	1,200	3.0	7.200	6.3815	+0.8185	+12
6	♂	100	60	60	1,380	2.85	9.600	7.120	+2.480	− 3
11	♀	167.5	70	65.25	2,048	2.58	10.400	7.101	+3.299	−14
13	♂	171	70	70	2,099	1.89	11.200	9.112	+2.088	− 7.5
11	♂	178	75	70	2,182	2.60	11.200	8.923	+2.277	+ −

* In this column, ♀ indicates female; ♂, male.

It is a well known fact that the body cannot be forced to store protein beyond its requirements. It is probable that if the metabolism experiment from which the figures in the last two tables were obtained was longer, the retention would fall. This fact indicates the uselessness of excessive protein in diabetic diets, but also would lead one to consider that

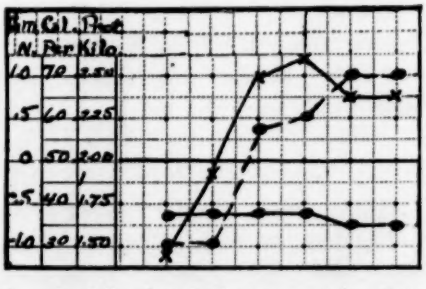

Chart 6.—Dotted and plain line indicates protein, dotted and broken line indicates calories and star and straight line indicates nitrogen retention.

the protein intake in these few cases, which was comparable to the values as given by Holt, was not greatly in excess of the body's requirements.

The determinations of the minimal and optimal amounts of protein required have all been done when the total caloric requirements are satisfied. The effect of failure to supply the energy needs with fat and carbohydrate on the protein required is shown in Chart 6.

The relative merits of carbohydrates and fats as protein sparers has been the subject of dispute for some years. Early investigators claimed that the nitrogen excretion rose when carbohydrate was replaced with isodynamic quantities of fat. More recently, Zeller,[24] from a large series of experiments on both men and animals, concluded that from 70 to 90 per cent. of the carbohydrate of the diet could be replaced by isocaloric amounts of fat without materially affecting the nitrogen excretion. In our experiments, variation in the distribution of the nonprotein calories between the fat and carbohydrate within the range allowable from their ketogenic-antiketogenic properties, had no noticeable effect on the minimal protein required.

Increased nitrogen excretion has been observed to follow added bulk to the diet. Van Slyke and Courtney [25] considered the decreased retention under such conditions as due to defective absorption resulting from

TABLE 4.—*Nitrogen Retention Unaffected by Bulk*

Protein per Kilogram	Protein in the Food				Bulk Grams	Nitrogen Excretion			
	Animal	Vegetable	Gelatin	Total	Vegetables and Fruits	Per Cent. Amount	Stool	Total	Balance
1.4	40.15	5.95	2	48.15	Less than 300	83	0.486	8.509	—0.509
1.7	48.3	6.00	2	56.30	200-300	85	1.060	8.223	+1.377
1.89	56.8	5.3	0	62.10	350	91	0.611	9.112	+2.088
1.59	57.0	6.7	0	63.70	350	90	0.821	7.489	+2.111
1.34	44.73	7.0	0	71.73	450	62	0.480	7.275	+0.725
1.00	29.0	6.0	2	37.00	450	79	0.676	8.244	—1.844
0.80	30.0	6.5	2	38.50	450	78	0.923	9.777	—3.377
1.69	37.3	6.7	0	44.00	550	84	2.850	5.937	+0.463
1.69	39.3	5.1	2	46.40	350	84	1.508	5.593	+0.807
1.60	31.8	8.65	2	42.45	550	75	1.799	7.030	—0.630
	38.85	7.0	0	45.85	250	86	1.101	5.807	+0.593

hasty passage of the intestinal contents. In the following experiment (Table 4) the nitrogen retention was unaffected by the bulk.

Bulk is indicated by the number of grams of vegetables and fruits, as the diets otherwise were identical.

CARBOHYDRATES

The primary inability of the diabetic patient to metabolize carbohydrates makes their restriction the one universally accepted principle of dietetics in the treatment of this disease. It is perhaps less generally recognized that, in computing the total glucose content of a diet, both proteins and fat must be considered with the carbohydrate as sources of glucose. Every hundred grams of protein may yield fifty-eight grams of glucose during its metabolism, while 10 per cent. of the fat in the form of glycerol is to be regarded as carbohydrate. The total carbohy-

24. Footnote 21.

25. Van Slyke, D. D.; Courtney, A. M., and Fales, H. L.: Forms of Nitrogen in Stools of Infants, Am. J. Dis. Child. **9**:533-541 (June) 1915.

drate intake of a patient, therefore, consists of 100 per cent. of the carbohydrate plus 58 per cent. of the protein, plus 10 per cent. of the fat in the diet.

Carbohydrates serve no specific nutritive function, so that consideration of the needs of the young for these foodstuffs is governed by the same rules as in the adult. Their chief function in the diet is as a source of energy, and in this way they act as nitrogen sparers. As has been pointed out in the foregoing, they may be replaced by isodynamic quantities of fat, provided they are not reduced too low to furnish 10 per cent. of the caloric intake. In diabetes they are equally important in the prevention of acidosis, fat being incapable of complete oxidation in their absence. The minimal amounts needed for this purpose depend on the proportional distribution of calories between the three classes of foods as well as on the actual carbohydrate content of the diet. The comment on the minimal allowance of carbohydrate is involved in the consideration of the maximal fat that may be safely allowed, so receives more detailed consideration.

FAT

There is a tendency at present to revert to the dietetic principles of the past generation in the treatment of diabetes. Restriction of carbohydrates and protein, plus a liberal allowance of fat to supply energy, characterized most of the diets given. Newburgh and Marsh [26] on this continent and Petrén [27] abroad both have reported good results on diets with small amounts of carbohydrate and protein and large quantities of fat. The latter gives excessively large amounts of fat, from 113 to 320 gm. daily and claims that his treatment is particularly beneficial in severe and marked acidosis. As Allen [28] has pointed out, the criterion of severity Petrén uses would exclude all but rather mild cases, and his mortality rates in such do not provoke enthusiasm. Newburgh and Marsh, however, give only sufficient fat to make up the caloric requirement when the patient is receiving two-thirds gram of protein per kilogram of body weight daily, and enough carbohydrate to make the diet palatable without exceeding the patient's tolerance. The availability of insulin at present renders the former great advantage of undernutrition of less value and would make a modification of the Newburgh and Marsh type of diet appear most suitable. These observers [29] have also pointed out an advantageous reduction of the endogenous protein metabolism when ample fat is given.

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26. Newburgh, L. H., and Marsh, P. L.: The Use of a High Fat Diet in Diabetes Mellitus, Arch. Int. Med. **26**:647-662 (Dec.) 1920; ibid, **27**:699 (June) 1921.
27. Petrén, quoted by Allen: J. Metabol. Res. **1**: 421, 1922.
28. Allen, F. M.: J. Metabol. Res. **1**:421, 1922.
29. Marsh, P. L.; Newburgh, L. H., and Holly, L. E.: Footnote 20.

Fear of producing acidosis by the use of much fat has acted as a deterrent to its general use, and has lately stimulated much research into the relationship between the intake of fat and ketogenesis. Shaffer [30] by in vitro experiments reached the conclusion that one molecule of glucose was ketolytic for one molecule of fatty acid. Later he [31] modified this conclusion, and stated one molecule of glucose to be capable of oxidizing two molecules of fatty acids. Woodyatt [32] and Hubbard and Wright [33] use a ratio of one of ketogenic to one of antiketogenic substances in their diets. Joslin [34] states that if the urine is sugar free and the protein does not exceed 1 gm. per kilogram of body weight, three times as much fat as carbohydrate may be given. Campbell [35] established a ratio of 1.3 : 1 as suitable for most cases.

In determining such ratios between ketogenic and antiketogenic portions of the diet, all those substances capable of producing glucose must be included in the latter, and all sources of fatty acids in the former. The glucose portion of the mixture will therefore include, in addition to the preformed carbohydrate, 58 per cent. of the protein and 10 per cent. of the fat which forms glycerol. Some dispute as to the antiketogenic power of the latter compared with glucose has arisen, but for the present it is considered with the glucose. The ketogenic value of a diet is obtained by adding 90 per cent. of the fat and 46 per cent. of the protein.

In our cases, a ratio of fatty acids to glucose of 1.5 : 1 has proved satisfactory in most instances. At times a lower ratio has been necessary to avoid ketonuria, but we have never found it possible to give more than this amount of fat without producing a more or less constant excretion of acetone bodies. It is, of course, very probable that the use of smaller amounts of protein would permit the use of larger quantities of fat. There is, however, no justification for such a proceeding. On ratios of 1.5 : 1 most children have acetonuria during an infection but it is not of a significant degree. It also occurs so frequently in normal children during infections that we do not regard it as a contraindication to the use of this quantity of fat. We have frequently noted the onset of ketosis with the resumption of normal activity, which disappears in a short time without any treatment.

INITIAL DIET

Progress in the treatment does not really start until the patient becomes aglycosuric and the blood sugar normal. The quickest way to

30. Shaffer, P. A.: J. Biol. Chem. **47**:433, 1921; ibid, **48**:449, 1921.
31. Shaffer, P. A.: J. Biol. Chem. **50**:26, 1922.
32. Woodyatt, R.: Footnote 7.
33. Hubbard, R. S., and Wright, F. R.: J. Biol. Chem. **50**:361 (Feb.) 1922.
34. Joslin: Treatment of Diabetes, footnote 3.
35. Campbell, W. R.: Canad. M. A. J. **13**:487 (July) 1923.

reach this stage would therefore seem indicated. This we have found to be best accompanied by placing the patient on a starvation diet for a day, using insulin if the blood sugar is excessively high. This method offers a further advantage in that while gradual increments in the diet are made, the patient's tolerance is determined. In the mild cases it is equally satisfactory to give them their basal requirements, alone or with insulin until sugar free. During this period of low diets less fat than before mentioned as suitable for the final diet should be given.

FINAL DIET

The final diet is to be determined by the child's nutritional needs and not by his tolerance. Sufficient insulin is given to render the extra food utilizable and to maintain the blood sugar at a normal level. The caloric

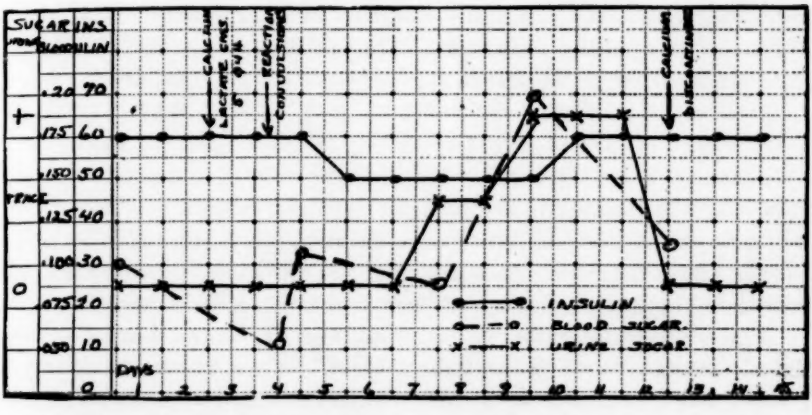

Chart 7.—This chart shows that the calcium lactate given caused but transitory reduction in the amounts of insulin needed.

requirement is determined by allowing the calories as estimated by Holt for the expected weight of the child, or by giving him twice the expected basal requirement. The results obtained by the two methods is almost the same. The protein requirement is determined by allowing from 2 to 3 gm. of protein per kilogram of expected weight, depending on the age of the child. The remaining calories are distributed between fat and carbohydrate in proportion, giving a ketogenic antiketogenic ratio of 1.5 : 1, unless a lower ratio has been proved necessary.

MEDICATION

Drugs for the most part have been relegated to the background by improvement in the dietetic treatment of this disease. Certain recent researches, notably those of Underhill,[36] and more lately of McCann and

36. Underhill, F. P.: J. Biol. Chem. **25**:447 (July) 1916.

Hannon [37] at Johns Hopkins Hospital, have given a certain amount of scientific explanation for the beneficial results claimed from the medieval feeding of ground egg shells and the more modern mineral springs treatment. These observers gave calcium hexos phosphate per os to a number of diabetic patients, and thereby caused an increase in the respiratory quotient. They also found it was more readily oxidized by the diabetic patient than glucose, but considered its use impracticable for physical reasons. Garofano and Labin [38] have claimed that calcium lactate stimulated pancreatic secretion. Calcium lactate has been given in large doses to a number of patients at the Hospital for Sick Children, and caused consistent but transitory reductions in the amounts of insulin needed to produce like results.

Medicines on the whole should only be mentioned to be condemned. Warning must be given that most medicines are made up in a vehicle containing sugar and should not be used indiscriminately. Purgatives are not often needed on the full diet, but mineral oil is recommended as the best when one is indicated.

HYGIENIC TREATMENT

Adequate rest is essential. The diabetic child should not be allowed continually to exercise to the point of fatigue. Such a course not only increases the metabolism but renders the child more susceptible to infections. The activities of a normal child are allowable, provided the rest considered optimal for such children, or possibly a little more, is taken.

Passive exercise plays no small part in the correction of certain defects in the posture of the diabetic child. When the disease has been present more than a few months, either untreated or maltreated, the abdomen becomes protuberant. This may readily be corrected by the use of suitable abdominal exercises or massage. Stretching exercises appear to hasten the growth in the length of dwarfed diabetic children, whose growth has been stunted for a long period because of insufficient nutriment.

All foci of infection should be removed early. Constant absorption of toxin depresses the food tolerance, and the presence of such foci greatly increases the incidence of intercurrent infections, of which the depressant action on the pancreas is well known.

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37. McCann, W. S., and Hannon, R. R.: Bull. Johns Hopkins Hosp. **34**:43, 1923.

38. Garofano, and Labin, B.: Compt. rend. Soc. de biol. **88**:1238, 1923.

A COMPARISON OF THE EVOLUTION OF CARPAL CENTERS IN WHITE AND NEGRO NEW-BORN INFANTS*

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NEW YORK

During the last few years, studies of the development of the carpal centers of children have been numerous. To this end roentgenograms have been employed, and have been the means of providing much more reliable and valuable information than the old anatomic method. As a result of these roentgenologic investigations, we have acquired considerable new information as to the period of development of the individual centers, and have learned to recognize various factors which tend to delay or to hasten their appearance. Hardly any of these studies, however, concern themselves with the evolution of the centers at the time of birth. They consider the question of calcification during later infancy and early childhood and treat more particularly of the relation of early or belated mental development to the evolution of the centers. In most of these inquiries the factor of sex is not taken into consideration. The data of the more important of these studies are reproduced in tabular form in a recent article by Scammon.[1] As he states, the most satisfactory investigation is that of Pryor,[2] which was carried out on American children and for this very reason has additional value for us. Pryor recognized the fact that the female infant is relatively precocious in its development of carpal centers; that whether we regard the question from the point of view of relative age or of length, the female baby develops these centers at an earlier period than the male. His figures for the development of the first center, which almost invariably is that of the os capitatum (magnum), is between the third and the sixth month for the female and between the fourth and the tenth month for the male. Attention should be called also to a recent comprehensive study of this subject by Stettner,[3] who likewise noted the comparatively early development of centers in the female. This investigation is of additional interest as it devotes particular attention to the social status of the children. Stettner found that the

* Received for publication, Dec. 26, 1924.

* From the Department of Pathology and the Sloane Hospital for Women, Columbia University.

1. Scammon, R. E.: Summary of the Anatomy of the Infant and Child, Abt's Pediatrics, Philadelphia, W. B. Saunders & Co., **1**:257, 1923.

2. Pryor, J. W.: Bull. State College of Kentucky, 1906; Bull. Univ. of Kentucky, 1908.

3. Stettner, E.: Arch. f. Kinderh. **68**:342, 1921.

rural child shows the slowest and the city child the most rapid evolution of the carpus. His tables, however, include almost no new-born infants and are therefore of little value in relation to the data which we have gathered.

ORIGINAL INVESTIGATION

Our work was undertaken in connection with a comprehensive investigation of the rickets problem. Some time ago we carried out a study of the development of the carpal centers in young rats, in order to ascertain whether this criterion would be of value in judging the effect of antirachitic factors in the diet of the mother or of the young. Although this study yielded some interesting results, it was found that the centers developed so rapidly in rats and that the interval between their appearance is so short that it is difficult to draw a distinction between normal and delayed calcification. This investigation, however, led to an inquiry regarding the centers in the new-born infant. In view of the fact that the negro is particularly susceptible to rickets, and that both in man and in animals growth is an important factor in the pathogenesis of this disorder, it seemed worth while to inquire whether there is any difference between the negro and the white race in the time of appearance of the carpal centers. An excellent opportunity to carry out a study of this kind was afforded by the Sloane Hospital for Women, which cares for about one-third negro women and two-thirds white women in its obstetric wards. These women are all of about the same social status. Accordingly, roentgenograms of the wrists were taken of all infants before the mothers were discharged from the hospital, usually when the babies are 12 days old. There was no selection of cases, although for various reasons from time to time some infants could not be examined. In all, about 500 new-born infants were roentgenographed in the course of the year, extending from November, 1923, to November, 1924. The accompanying charts and figures furnish a summary of our results. It will be noted that the infants are classified according to race, according to sex and according to size. In regard to size, a distinction was made between the full-term infant ("normal") and the premature or small infant. An arbitrary boundary was drawn which placed all infants shorter than 48 cm. in length or weighing less than 6 pounds in the group of premature or small infants. A special table has been constructed for twins and another for normal infants classified according to their birthweights.

When we consider the factor of race, it is evident that centers were present far more often among the negro than among the white new-born infants. Among the 131 negro babies, centers were observed in thirty-seven, or in 28 per cent. of the cases, whereas among the 212

white babies centers were observed only in thirty-three cases, or in 10 to 11 per cent. of the cases. This relative precocity is perhaps more striking in the accompanying figure (Chart 1) than in the table (Table 1). That the difference is not due to the factor of sex, to a preponderance of females among the negroes, is apparent from the study of this table and Chart 2. These show that, although there were exactly one-third more white female infants than negro female infants, carpal centers were present in twenty-five of the negro infants and in only twenty-one of the white infants. The same distinction holds true in regard to males; twelve cases with centers among sixty-nine male negro infants as com-

TABLE 1.—*Carpal Centers in Full-Term New-Born Infants*

Negro Infants					White Infants				
Total				131	Total				212
Male				69	Male				119
Female				62	Female				93
	No. of Centers					No. of Centers			
	1	2	3			1	2	3	
With centers				37	With centers				33
Male	6	6	0	12	Male	6	6	0	12
Female	9	15	1	25	Female	6	15	0	21
Without centers				94	Without centers				179
Male				57	Male				107
Female				37	Female				72

TABLE 2.—*Carpal Centers in Premature and Small Infants*

Negro Infants		White Infants	
Total	34	Total	38
Male	15	Male	11
Female	19	Female	27
With centers	7	With centers	4
Male	5	Male	0
Female	2	Female	4
Without centers	27	Without centers	34
Male	10	Male	11
Female	17	Female	23

pared to twelve cases among 119 white males. No distinction was drawn between the intensity of color of the negroes, and it is quite possible that had we been able to limit our studies to those which sprang from purer negro stock, the difference between the white and colored babies might have been still more pronounced. It will be noted that in numerous instances two centers were present, especially in the female infants, whether negro or white. Where only one center was seen, it was symmetrical in all but three cases and always involved the os capitatum.

Table 2 furnishes similar information in regard to the premature and the small infants. The total numbers are not large but again there is

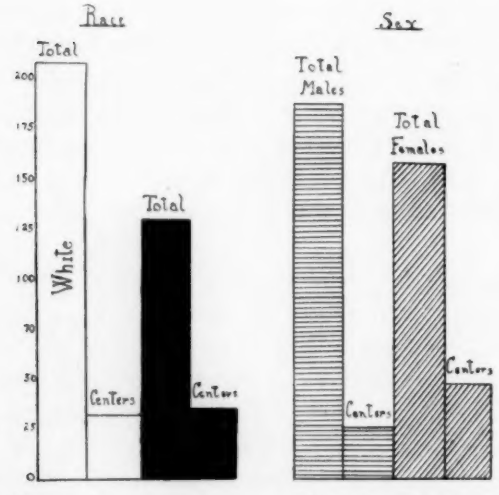

Chart 1.—Incidence of a carpal center at birth in full term infants. (*a*) white compared to negro infants (*b*) males to females.

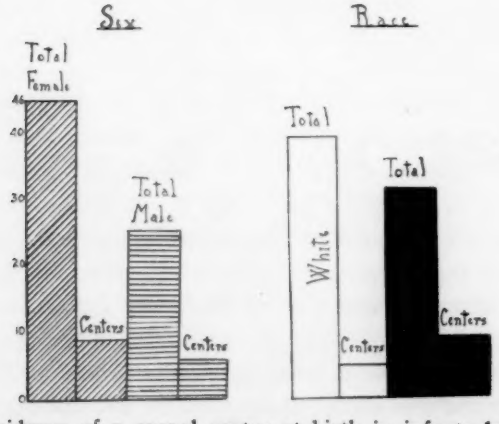

Chart 2.—Incidence of a carpal center at birth in infants less than 48 cm. in length or 6 pounds in weight; (*a*) males compared to females, (*b*) white to negro infants.

a comparative preponderance of centers among the negro infants, although this was not manifested particularly among the females. In Table 3 we have grouped together three sets of negro twins and three sets of white twin infants. This tabulation gives a more detailed picture of the data which furnished the basis of our study. In this connection it may be stated that about one-half of the negro mothers were born in the West Indies and one-half in the United States, mainly in the Southern States. In regard to the twins, it will be noted that

TABLE 3.—*Carpal Centers of Twin New-Born Infants*

Race	Sex	Centers	Date	Weight, Gm.	Length, Cm.	Pregnancy of Mother	Birthplace of Mother	Wassermann Reaction	Length of Puerperium
Negro	Male.....	0	11/ 8/23	2,200	46	I	Florida	Neg.	8½ mo.
	Male.....	0	.....	2,250	47				
Negro	Female.....	0	5/ 2/24	2,650	51	III	North Carolina	Neg.	9 mo.
	Male.....	0	.....	2,810	52.5				
Negro	Male.....	0	8/30/24	2,400	48	II	Florida	Neg.	9 mo.
	Female.....	2	.....	2,400	48				
White	Male*.....	0	2/ 8/24	3,000	..	III	Italy	Neg.	9 mo.
White	Male.....	0	3/ 2/24	2,700	47	II	.....	Neg.	8 mo.
	Female.....	0	.....	2,360	46				
White	Male.....	0	8/14/24	2,200	48	V	Ireland	Neg.	8 mo.
	Female.....	0	.....	2,200	48				

* Other twin died.

TABLE 4.—*Carpal Centers Grouped According to Birthweight of Infants*

	Negro Infants			White Infants		
	Weight, 2,720 to 3,100 Gm.	Weight, 3,100 to 4,000 Gm.	Weight, 4,000 Gm.+	Weight, 2,720 to 3,100 Gm.	Weight, 3,100 to 4,000 Gm.	Weight, 4,000 Gm.+
Total Cases:						
Male.....	41	24	4	48	62	9
Female.....	40	18	4	48	41	4
With Centers:						
Male.....	8	3	1	6	4	2
Female.....	13	9	3	8	12	1
Without Centers:						
Male.....	33	21	3	42	62	7
Female.....	27	9	1	40	41	3

only one infant showed carpal centers and that this one was a negro and a female.

Table 4 shows the incidence of carpal centers in colored as well as in white infants, tabulated according to birthweight. A classification into three groups was made comprising medium, large and exceptionally large infants. The numbers in the individual groups are not very large, and the only conclusion which can be drawn is that large babies are more prone to show an early development of centers than small babies. For example, in the group of large negro infants there were eighteen females, among which nine had carpal centers and in a similar group of white babies comprising forty-one cases, there were twelve females

who showed centers. This ratio is higher than that existing among the infants weighing less than 1,300 grams or among the normal infants tabulated in Table 1.

In view of the fact that it has been claimed that the first born is more likely to evince early development and differentiation, a table was framed to elucidate this point. As no distinction in this regard was evident, the table is not reproduced.

Furthermore, the entire group of cases was arranged according to the months of their birth, in order to note whether there was a seasonal factor in relation to carpal development, whether carpal centers are present to a greater extent in babies born in the spring or the summer months than in those born in the fall or in the winter. It was found that our data were insufficient to answer this question, owing to the fact that the subdivisions into twelve units rendered the cases too few in number and that there was a temporary interruption in the examinations at one or more periods during the year.

In a few instances the roentgenologic picture was suggestive of rickets. In one case it greatly resembled the early lesions that we are accustomed to see; this was a female white (Italian) infant which, when 7 months of age at the beginning of December, was found to have developed signs of slight rickets.

COMMENT

It is evident that a carpal center is present at birth far more often than we have been wont to believe. In male white babies we observed it in 10 per cent. of our series, and in female white babies in somewhat over 22 per cent. The difference in this respect between male and female babies has been noted in older infants by other observers. What we wish to bring out particularly is the fact that these centers are to be seen much more frequently in negro than in white babies. Among our cases of female negro babies, the incidence reached 40 per cent. This distinction is one which exists quite apart from the factors of sex or of birthweight. In respect to weight, conditions favored the white infants; for the larger the baby the more prone it is to develop centers early, and as may be seen from our figures, the birthweight of the white babies was decidedly greater on the average than that of the negroes (Table 4). It would seem that this difference in evolution of the centers can be accounted for only as a racial peculiarity. As is well known, the extremities of the negro are longer than those of the European. This is true during prenatal as well as throughout postnatal life. In his article on growth, Friedenthal [4] has shown by measurements

4. Friedenthal, H.: Ueber Wachstum, Ergebn. f. inn. Med. u. Kinderh. **2**:685, 1913.

and diagram that the arms and legs of a 60 gm. negro fetus were considerably longer than the extremities of a 60 gm. Europeaan fetus as compared to the length of the trunk. He found these typical growth characteristics of the negro manifested in a fetus 3½ months of age, in spite of the fact that pigmentation of the skin had not yet developed. In a table which gives in detail the dimensions of the human fetus he contrasts the length of various parts of the body of a European fetus and of a negro fetus 4 months of age. The arm of the former was 55.3 mm., of the latter 59.2 mm.; the leg of the former 49.6 mm. and of the latter 63.2 mm.; the foot 15 mm. as compared to 17 mm. in the negro fetus. The same differences are to be observed between the adult negro and the adult European. As Friedenthal expresses it: "Growth is hereditary throughout the entire span of life; intra-uterine growth follows the same laws as does extra-uterine growth."

It is difficult to judge whether this precocious maturity of the negro, this early development of carpal centers, bears a relationship to the remarkable susceptibility of this race to rickets. Although there is no doubt that pigmentation of the skin plays a rôle in this connection, it has never seemed to us that this factor was sufficient to account entirely for the marked difference in susceptibility between the two races. The well-known interrelationship between growth and rickets must be thought of in this connection, the fact that the more rapid the growth impetus, the greater the liability of the infant or of the experimental animal to develop rickets. This would help to explain the comparative susceptibility of the negro. A point which may seem to argue against this view is the fact that female infants develop centers earlier than do male infants, whereas rickets is supposed to occur as frequently in the one sex as in the other. Whether such is truly the case requires further investigation. It should be remembered that our conception of rickets has undergone a radical change during the last few years since we are able to recognize its earlier stages. Even now we are far from being able to diagnose it at its inception. The question arises whether an equal degree of susceptibility to rickets would be found in male and female infants in a large group which had been tested by the more refined clinical and laboratory methods.

CONCLUSION

It is by no means uncommon to observe by means of roentgenograms the presence of carpal centers in infants at the time of birth. This development was noted more frequently in female than in male infants, and was somewhat more frequent in heavier than in lighter babies.

Quite apart from the factors of sex or of weight, new-born negro infants, both male and female, showed calcification of the centers far more frequently than white infants. This is interpreted to be due to a racial difference.

The question whether this distinction in development and maturity bears a relationship to the well-known susceptibility of the negro to rickets is raised but cannot definitely be answered.

PROTEIN SENSITIVITY IN INFANTILE ECZEMA*

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The voluminous literature published during the last ten years, concerning the subject of allergy and its associated manifestation, has aroused a widespread interest in practically all branches of medicine. Clinical and laboratory studies of so-called hypersensitive subjects, made by numerous authors, with case reports and statistics showing encouraging results obtained by therapeutics, based on the information gleaned from cutaneous and intracutaneous tests has prompted others to apply this method in the treatment of those cases which might possibly be classified with the allergic group. Idiopathic headaches and pains, epilepsy and neuropathies, vertigos and obscure intranasal conditions are being investigated; also hay-fever, asthma, urticaria and food idiosyncrasies from a hypersensitive point of view. Pediatricians especially, have been interested since the demonstration by Schloss,[1] Blackfan,[2] O'Keefe[3] any many others, of the relation existing between protein sensitivity and infantile eczema.

CLINICAL RESULTS

With the object in view of determining what actual clinical results were obtained in those patients with eczema, treated solely in conjunction with the information obtained from the application of sensitivity tests, I have reviewed a series of 100 patients, selected from among those treated during the last four years at the Children's Memorial Hospital.

Only those types of true infantile eczema are considered. Patients with questionable histories, or in which the lesions might possibly be secondary to other skin conditions or to poor hygiene, are excluded. The forms varied from the mild localized erythematous types so often seen in breast fed babies to the generalized eczemas in which many or all types of lesions are seen.

Most of the tests were made by the scratch method, although intracutaneous injections were made in some cases. The latter undoubtedly

* Received for publication, Jan. 28, 1925.
* Read before the December meeting, Chicago Pediatric Society.
* From the Protein Sensitization Clinic, Children's Memorial Hospital.

1. Schloss, O.: Allergy in Infants and Children, Am. J. Dis. Child. **19**:433 (June) 1920.

2. Blackfan, K. D.: Cutaneous Reaction from Proteins in Eczema, Am. J. Dis. Child. **11**:441 (June) 1916.

3. O'Keefe, E. S.: Boston M. & S. J. **183**:569 (Nov. 11) 1920; ibid. **185**:194 (Aug. 18) 1921.

yields a slightly higher percentage of positive reactions, but there are several reasons that make the cutaneous tests more desirable in the particular class of patients dealt with.

1. Properly prepared, sterile solutions of proteins are difficult to make and are unstable.

2. Scarifications are obviously more easily performed on infants, who invariably cry and thresh about, making it difficult to keep the point of a needle between the layers of the skin.

3. Many mothers object to the needle puncture but are not adverse to the painless, almost imperceptible incisions.

The proteins used were manufactured by three commercial concerns, the majority of the tests being performed with proteins in dry powder form. In some instances certain foods, such as egg and milk, were applied in the natural state.

In making the scarifications, an attempt was made to produce uniform scratches 0.5 cm. in length, without the oozing of blood. A Pirquet borer was used in some cases. The amount of protein applied was that contained on the end centimeter of a round wooden Peerless applicator. To this was added one drop of a tenth normal sodium hydroxid solution.

The area chosen for scarification was usually the abdomen or back and sometimes the forearm. In testing a large number of subjects with a positive reaction, it was found that a reaction resulted regardless of the location of scarification, whether on the abdomen, the back or the arm.

In reading the result of the tests three factors were taken into consideration: namely, the presence of an area of erythema, the presence of a wheal and the length of time necessary to produce the before mentioned reactions. It was found that in some cases of suspected sensitivity, areas of erythema only were produced, no wheals appearing. When such a reaction resulted, the patient was given the benefit of the doubt and treated accordingly. The typical criterion of a positive test was found to consist of a wheal, irregular in outline and surrounded by an area of erythema. No standard was set for the size of a wheal necessary, but the reaction was compared with the control and other scarifications as to size and shape. Wheals are often produced by trauma alone or by the irritant action of the solutions employed, especially in children, but these wheals are relatively smaller and are regular in outline and may or may not be surrounded by erythema.

The length of time necessary for the appearance of a positive reaction is chiefly of importance in determining which protein is to be investigated first. When several positive reactions appeared, it was almost invariably the protein that produced the most rapid reaction also resulted in a larger wheal formation.

Practically all children with positive reactions were retested several times, and if practicable the protein was applied in the natural state. Doubtful cases were always retested, to eliminate the possibilities of error.

Since all of the patients were infants, therapeusis based on the reduction or elimination of the specific proteins was easily accomplished, except in the case of milk. In breast-fed babies, who gave positive reactions to elements contained in the mother's diet, it was considered justifiable in some cases to change the food to other forms of milk which might not contain the offending proteins.

Artificially fed infants coming under observation were immediately placed on limited dietaries and tested for those foods ingested. Positive reactions were eliminated so far as possible, and only those foods given which produced negative skin reaction. If, after sufficient observation, the eczema persisted, other foods were eliminated from the diet successively. One was able to observe then, not only the effect of elimination of positively reacting elements but also that produced by the absence of negatively reacting foods from the diet. It was impossible, of course, to eliminate milk entirely for any length of time, but when necessary, this food was reduced to a minimum and the deficiency in calories and to some extent in protein, made up with carbohydrate, vegetable and fruit. Realizing, as have others, that in eczema the condition often improves when milk is changed by boiling, drying or by other means, the infant was sometimes given dried milk or evaporated milk, protein milk, lactic acid milk, synthetic milk or peptonized milk.

It has been my observation that eczema, for reasons known or unknown, often will improve rapidly, so that in the course of a few days a skin that was formerly entirely covered with severe eczematous lesions will appear quite normal with no sign of the former inflammation and infiltration. So it has appeared to me that if any food or food elements were responsible, elimination of the offending factor should be followed by more or less definite improvement in four or five days' time. With this idea in view, most of the patients were seen at weekly intervals and changes made according to clinical manifestations.

LOCAL TREATMENT

Local treatment was reduced to a minimum, and whenever possible withheld for variable periods so that the effects of food elimination might be observed without interference of local therapy. In most instances it was found necessary eventually to institute local treatment, in order to encourage the patient's return.

AGE OF ONSET

The average age at the time of coming under observation was 5 months and 2 weeks. The average age of onset, according to histories,

was 2½ months. In fifty-seven patients the eczema began while the infant was still exclusively breast fed, in twenty-three after other food, usually cow's milk, had been added to the diet. Eleven infants had never been breast fed and in nine there was a doubtful history as to the time of onset. The youngest infant treated was 3 weeks old and the eldest 1 year.

None of the infants were under observation for less than five weeks, and of the group seventeen have been seen from time to time for periods varying from one to four years.

An enumeration of the proteins tested for appears in Table 1, with the number and percentage of positive reactions in each group. Since each infant was put on a limited diet, the number tested for could be

TABLE 1.—*Reactions to the Tests*

Proteins	No. Tested	No. Positive	Per Cent.	Proteins	No. Tested	No. Positive	Per Cent.
1. Milk, mothers, fresh	25	0	0	27. Peas	48	3	6
2. Milk, cows, fresh	43	11	25	28. String beans	26	2	7
3. Milk, cows, boiled	21	9	42	29. Beet	34	3	8
4. Milk, dried	24	7	29	30. Lettuce	20	0	0
5. Milk, protein, commercial	100	8	8	31. Tomato	44	6	13
6. Casein	28	4	14	32. Spinach	22	2	9
7. Lactalbumin	28	7	25	33. Asparagus	8	0	0
8. Milk, goat, protein	3	0	0	34. Turnip	5	0	0
9. Egg white, fresh	36	21	67	35. Celery	12	0	0
10. Egg yolk, fresh	36	17	47	36. Onion	20	1	5
11. Egg white, protein	100	21	21	37. Cabbage	14	0	0
12. Egg yolk, protein	100	17	17	38. Prune	34	0	0
13. Egg-ovo mucoid	10	8	80	39. Apple	28	0	0
14. Egg-ovo vitellin	10	6	60	40. Orange	58	4	6
15. Wheat, whole	100	8	8	41. Peach	10	0	0
16. Wheat, gliadin	14	0	0	42. Pear	8	0	0
17. Wheat, globulin	14	2	14	43. Plum	4	0	0
18. Wheat, gluenin	14	1	7	44. Pork	38	6	15
19. Wheat, proteose	14	1	7	45. Beef	42	8	9
20. Wheat, leucosin	14	1	7	46. Lamb	34	4	11
21. Oat	100	6	6	47. Chicken	28	3	10
22. Barley	100	5	5	48. Coffee	15	1	6
23. Rye	31	2	6	49. Banana	5	0	0
24. Rice	17	2	11	50. Peanut	6	0	0
25. Corn	9	0	0	51. Cheese	8	1	12
26. Carrot	53	5	9	52. Potato	54	3	5

considerably reduced, while in the case of breast-fed infants the mother's dietary was subjected to a close scrutiny for unusual or unsuspected food elements.

Statistics and figures are often misleading unless one is familiar with their compilation, and so in studying Table 1 an explanation is necessary in order to forestall false conclusions. Practically all patients who gave a positive reaction to milk protein were retested with other forms of milk and with the individual constituents of milk. So the only figures which have real significance, from a percentage point of view, are those relating to the tests made with commercial milk protein. This is true also of egg and some of the cereals. Again, many times certain proteins were applied because of a history which suggested aggravation of symptoms, or even true food idiosyncrasy with vomiting, and other

manifestations on ingestion of certain food elements. This reaction is noted especially with tomatoes. Two infants vomited repeatedly after taking tomato juice, and with such encouragement a relatively large number of infants were tested for a reaction with tomato.

ROUTINE TESTS

However, routine tests were made with milk and cereals, since these constituted staple articles of diet and all babies were tested for egg because of the high percentage of positive reactions obtained. It is interesting to note that only 8 per cent. of positive reactions to milk were recorded, in spite of the common clinical observation that large amounts of milk often aggravate eczema. Wheat showed 8 per cent. of positive reactions, while potato, which has been reported by other authors as a common offender, showed only 3 per cent. The meats all gave a relatively high percentage, although few of the artificially fed infants gave a history of ingestion of such food.

Of the 100 infants tested, there were positive reactions in fifty-three and negative reactions in forty-seven. The percentage of negatives are

TABLE 2.—*The Percentage of Positive Reactions Recorded by Various Observers*

Observers	Subjects	No. Cases	Per Cent. Negative
Schloss	In infants under 16 months	53	24.5
O'Keefe	In infants	70	24.5
Blackfan	In children	27	18.5
White	In children	56	20.0
Herman	In infants and children	30	43.0
Sidlick and Knowles	In infants and children	23	35.0
Corper	In infants under 1 year	100	47.0

rather high, compared to the figures in Table 2, but when one considers the ages of the infants this is not unusual. In many cases reactions to several proteins were obtained, and many of the positive reactions were obtained with foods which had never been included in the diet of either the mother or the baby.

Nineteen infants showed reactions to one protein only, and thirty-four to more than one protein. One infant, not recorded here, gave reactions to seven proteins, six of which had never been ingested.

Of the fifty-three infants showing positive skin tests, only 38 were found to be proper subjects for this study. The remaining fifteen were rejected chiefly because it was impossible to reduce or eliminate the offending protein, especially in breast-fed subjects, because of poor cooperation, or because other therapeutic measures were resorted to.

Table 3 shows the results obtained in treating breast-fed infants; five patients showed more or less improvement and in only one did the eczema entirely disappear; one infant, Case 1 B, showed improvement only after being weaned and given dried milk, although there was a positive reaction to cow's milk and not to breast milk; two infants,

TABLE 3.—*Results Obtained by Elimination of Specific Proteins in Breast-Fed Infants*

Case	Age, Mos.	Reactions	Therapeutic Measures	Results: Improved	Results: Cured
1B	3	Egg white Egg yolk Milk, cow's Wheat, whole Wheat globulin	1. Foods eliminated from mother's diet... 2. Three substitute feedings of dried milk 3. Weaned, dried milk feedings.....	1. No change 2. Improved 3. Improved	No
2B	5	Peas	1. Food eliminated from mother's diet....	1. No change	No
3B	1	Egg white Egg yolk	1. Food eliminated from mother's diet.... 2. Weaned, given cow's milk and cane sugar	1. Slight improvement 2. Slight improvement	No
4B	5	Egg white Egg yolk	1. Foods eliminated from mother's diet... 2. Weaned, given cow's milk, dextrimaltose and cereals	1. Improved 2. Improved	No
5B	7	Milk, cow's Egg white Egg yolk	1. Foods eliminated from mother's diet... 2. Weaned, given goat's milk.....	1. Slight improvement 2. Slight improvement	No
6B	2	Oats	1. Foods eliminated from mother's diet...	1. No change	No
7B	4	Tomato	1. Food eliminated from mother's diet... 2. Weaned, given cow's milk, cereal and cane sugar 3. Tomato added to diet.....	1. Cured 2. Cured 3. Cured	Yes
8B	8	Milk, cow's Lactalbumin Casein	1. Foods eliminated from mother's diet...	1. Improved	No
Total.....				6	1

TABLE 4.—*Results Obtained by Elimination of Specific Proteins in Breast-Fed and Bottle-Fed Infants*

Case	Age, Mos.	Reactions	Therapeutic Measures	Results: Improved	Results: Cured
1BA	10	Egg white Egg yolk Beef Pork Lamb	1. Eliminated from mother's diet..... 2. Weaned	1. Improved 2. Improved	No
2BA	4	Wheat, whole Wheat globulin Wheat protein	1. Eliminated from mother's and infant's diet	1. No change	No
3BA	9	Peas Potato Beet	1. Weaned	1. No change	No
4BA	9	Egg white Egg yolk Beef	1. Eliminated from mother's and infant's diet	1. Improved	Yes
5BA	3	Oat Onion	1. Eliminated from mother's diet.....	1. No change	No
6BA	8	Beet Tomato	1. Eliminated from mother's diet.....	1. No change	No
7BA	2	Oat	1. Eliminated from mother's diet.....	1. Improved	No
8BA	5	Egg white Egg yolk	1. Eliminated from mother's diet..... 2. Weaned	1. Improved 2. Cured	Yes
9BA	6	Carrot String beans Spinach	1. Eliminated from mother's diet.....	1. No change	No
Totals.....				4	2

Cases 3 B and 4 B, were positive to egg alone, but the condition did not entirely clear up even after being weaned and placed on an egg-free diet. It is interesting and incomprehensible, from an allergic point of view, that Case 7 B, who was entirely relieved of symptoms only after weaning,

TABLE 5.—*Results Obtained by Elimination of Specific Proteins in Artificially Fed Infants*

Case	Age, Mos.	Reactions	Improved		Results	
			Temporary	Permanent	Improved	Cured
1A	2	Wheat, whole Wheat, leucosin Potato	Yes	No	No	No
2A	8	Orange	No	No	No	No
3A	8	Rice	Yes	No	No	No
4A	9	Milk, cow's Egg white Egg yolk Beef	Yes Milk reduced	Yes	Yes	Yes
5A	3	Barley Egg white Egg yolk	Yes	Yes	Yes	No
6A	12	Tomato Orange	No	No	No	No
7A	7	Wheat, whole Spinach	Yes	Yes	Yes	No
8A	4	Wheat, whole	Yes	No	No	No
9A	3	Milk, cow's Wheat, whole Barley	Yes Milk reduced	Yes	Yes	Yes
10A	3	Milk, cow's	Yes Given milk boiled 1 hour	Yes	Yes	Yes
11A	11	Egg white Egg yolk Beef Lamb	Yes	Yes	Yes	Yes
12A	2	Lactalbumin	Yes Milk reduced and boiled	Yes	Yes	No
13A	5	Orange	No	No	No	No
14A	3	Wheat, whole	Yes	No	No	No
15A	5	Oat	Yes	Yes	Yes	No
16A	4	Casein Oat Egg white	Yes Dried milk used	Yes	Yes	No
17A	7	Egg white String beans	Yes	No	No	No
18A	6	Carrot Egg white Egg yolk	No	No	No	No
19A	10	Egg white Egg yolk	Yes	Yes	Yes	No
20A	1	Lactalbumin	Yes Given evaporated milk	Yes	Yes	No
21A	2	Barley Rye	Yes	No	No	No
Totals.....			17	11	11	4

showed no return of the eczema after being given a large ration of tomato juice daily. Cases 2 B and 6 B, in whom improvement should logically be expected by elimination of peas and oats, respectively, showed no change.

Reactions and results in breast-fed infants who received additional food, usually cow's milk, cereal and fruit, are shown in Table 4. Two infants, Cases 1 BA and 7 BA, were improved and two infants, Cases 4 BA and 8 BA, cured. It is significant that those infants, both in this table and in the preceding one, who were sensitive to egg protein and the animal proteins, were more likely to be benefited by elimination than those who were positive to cereals or vegetables.

In Table 5 are listed twenty-one artificially fed infants, some giving positive reactions to foods not contained in the dietary and in several instances, to foods which could not have previously been derived through the breast milk since the infants had never been nursed. Seven infants showed clinical improvement and four were apparently cured. Two infants who showed improvement, Cases 7 A and 15 A, were sensitive to cereals and vegetables, and Case 5 A may have been sensitive to barley, since egg was not a part of the diet. Of those patients entirely relieved, all were sensitive to animal proteins, which corresponds to the results in the two preceding tables.

TABLE 6.—*The Results of Specific Treatment Obtained by Others*

Observers	Subjects	Percentage	
		Cured	Improved
O'Keefe	Breast-fed infants	40	20
Herman	Infants and children	45	55
Sidlick and Knowles	Infants and children	40	60
Shannon	Breast-fed infants	74	13
Corper	Infants	18	37

In summing up the results in Tables 3, 4 and 5, we find that of thirty-eight infants with eczema who are treated by eliminating or reducing the offending element, there is improvement in fourteen, or 37 per cent., and a definite subsidence of symptoms in seven or 18 per cent. When one stops to consider the clinical course of infantile eczema, marked by frequent remissions and exacerbations, with changes in the cutaneous manifestations coincidental with changes in the diet, changes in the temperature or external conditions or with the onset of acute infections, one wonders what part of these improvements and apparent cures were due to the idiosyncrasies of eczema and what part real. Unfortunately, it was not always possible to check up results by feeding the offending protein to those infants showing improvement, and no statistics are given concerning the few patients in which this was done. However, the object of this summary is to evaluate properly the practical worth of cutaneous sensitization tests in infantile eczema, rather than discuss the specificity of protein involved in each particular instance.

That the foregoing results are low in comparison to those obtained by other authors, may be seen by comparison with the results obtained

by other investigators in Table 6. It is difficult to know the part played by external remedial agents in producing improvement in some of the patients cited by other authors, and no one familiar with eczema can deny that the cooperation of the dermatologist is a valuable asset.

In connection with the large percentage of improvements occurring on elimination or reduction of animal protein, it is significant that Czerny,[4] about twenty years ago, observed that milk was not a particularly good food for infants with so-called exudative diathesis. Blackfan [5] observed that severe eczema would often disappear after reduction or elimination of milk from the diet, and Schloss [1] found that six patients who were given a mixture consisting of protein-free milk, washed butter and soy bean protein improved markedly in twenty-four hours. Blackfan [5] advises that patients who are susceptible to a combination of proteins should be placed on a diet free of egg, meat and milk, even though no positive tests to these foods appear. He adds that the reason for so doing is more or less empirical.

COMMENT

When one compares the results in the foregoing tables with those obtained in true cases of food idiosyncrasy, one is impressed with the fact that in the idiosyncrasies a positive reaction is practically always obtained to those foods causing manifestations. This may be explained on the assumption that in such cases there is an extremely low tolerance or threshold for the food giving rise to symptoms, while in eczema the infant may have a limited tolerance to single proteins or to a combination of proteins. Or it is quite within reason to suppose that eczematous infants suffer from the cumulative action of such proteins, to which there is sensitivity only in degree.

That specific proteins are the sole etiologic factors in the production of eczema is yet to be proved, and most certainly the proof offered up to the present is insufficient on which to base conclusions. That, however, positive cutaneous tests are associated with infantile eczema is beyond question, but at present we must regard this relationship as a guide to diagnosis and treatment and as a possible stepping stone to the discovery of the actual etiology.

SUMMARY

Infants with eczema show a high percentage of positive skin tests to proteins, which may or may not be included in the dietary.

Elimination of the specific proteins is conducive to subsidence of symptoms in only a relatively small percentage of cases.

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4. Czerny, A.: Jahrb. f. Kinder. **61**:199, 1905; ibid. Monatschr. f. Kinderh. **6**:9, 1907.

5. Blackfan, K. D.: Protein Hypersensitiveness in Children, Am. J. M. Sc. **160**:350 (Sept.) 1920.

Improvement of clinical manifestations, rather than complete recovery, may be expected in those patients who are benefited.

Patients sensitive to animal proteins are more likely to respond to specific treatment than those sensitive to cereals, fruits and miscellaneous proteins.

The presence of a positive cutaneous test is not a criterion to the successful treatment of infantile eczema.

A CASE OF TYPHOID PERITONITIS IN AN INFANT WITHOUT INTESTINAL PERFORATION *

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AND
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A careful search of the literature reveals the fact that only fifty odd cases of peritonitis during the course of typhoid fever without intestinal perforation have been thus far reported. All were in adults except one, which was reported by Wilson,[1] in 1886. His patient was a child, aged 12 years. No reports of the occurrence of this condition in infants having been found, we believe it to be of interest to report the clinical course of such a case.

REPORT OF CASE

B. H., Jewish, aged 16 months, was first seen on Oct. 5, 1924, in consultation with the family physician, and the following history was obtained. The child first became ill on September 28, with vomiting, loss of appetite and a sudden elevation of temperature to 104 F. The stools were evacuated once a day, were of good color and normal consistency. Physical examination during the entire period from September 20 to October 5 revealed nothing. The temperature fluctuated between 101 F. in the morning and 104 F. in the afternoon. Physical examination on October 5 revealed no positive findings, and it may be definitely stated that there was no enlargement of the spleen, although especially looked for. Owing to the fact that the child had had an attack of pyelitis at 6 months of age, a specimen of urine was examined for pus cells and found to be negative. The possibility of typhoid fever was now considered. Physical examination on October 6 revealed nothing different from the previous day. The white blood count was 5,200, with 65 per cent. lymphocytes; mononuclears, 6 per cent.; polymorphonuclears, 27 per cent., and eosinophils, 2 per cent. The Widal test was negative. The case was considered one of typhoid fever, however, because of the leukopenia and continuous elevation of temperature. On October 13, the infant had an attack of vomiting and went into collapse; the abdomen became suddenly distended. The baby had several attacks of vomiting during the night. Examination at this time revealed the following: the child was slightly cyanotic, was extremely restless and had an anxious expression. The heart and lungs were negative. The abdomen was markedly distended and the superficial veins of the lower part of the chest and the upper part of the abdomen were engorged. Tenderness and rigidity were present over the entire abdomen. There was shifting dulness in both flanks and a fluid wave could definitely be elicited. There was no absence of liver dulness and the spleen was palpable at this examination. On the lower chest wall and the upper portion of the abdomen, there now were scattered rose spots. A diagnosis of general peritonitis following perforation of the intestines from a typhoid ulcer was made and immediate hospitalization was advised. The child was admitted to my service (H. M. G.) at the United Israel Zion Hospital at 5 p. m. of the same day, where a blood examination showed a white cell count of 27,600 with 78 per cent. polymorphonuclears and 22 per cent. lymphocytes. Immediate opera-

* Received for publication, Jan. 6, 1925.

* From the Pediatric Service of the United Israel Zion Hospital.

1. Wilson, J. C.: Philadelphia Medical Times, Dec. 11, 1886.

tion was advised and was performed by Dr. William L. Wolfson. His report of the operation was as follows: A high right rectus incision was made. The peritoneal cavity was opened and a large amount of serous fluid escaped. The appendix was located and found to be normal. No intestinal perforations were visible. The peritoneum showed evidence of an acute inflammatory reaction. After evacuating the fluid, the wound was closed in the usual manner. Two cigaret drains were inserted. The infant from this time on made an uneventful recovery.

October 14, the blood showed a positive Widal in dilutions of from 1:80. Examination of the fluid from the peritoneal cavity revealed the following: the fluid was clear, transparent with a yellowish tint and sterile on culture. Widal test, under microscope, showed strong agglutination in from 1:80 dilution. Other laboratory examinations made were as follows: October 16, the white blood count was 20,800 with 68 per cent. polymorphonuclears and 32 per cent. lymphocytes. The blood culture on October 17 was sterile. The intracutaneous tuberculin test made on October 17, with 0.2 c.c. of a 1:1,000 mg. tuberculin was negative. A white blood count on October 21 showed 16,400 cells, with 73 per cent. polymorphonuclears and 27 per cent. lymphocytes. Cultures from the stool made on October 31, November 6, November 20, and November 27 were negative for typhoid. The urine at all times was negative.

COMMENT

Because of the character of the effusion and because no perforation was found at the time of operation, it was at first thought that we were dealing with a combination of typhoid and tuberculous peritonitis. Because of the following facts, however, we discarded this diagnosis; first, that the peritonitis occurred suddenly; second, that the peritoneum showed no tubercles; third, that there were no tubercle bacilli in the effusion; and finally that the child reacted negatively to the Mantoux test. Most cases of peritonitis occurring during the course of typhoid are due to perforation. In our patient this could not be the case, because first there was no perforation to be seen when the intestine was exposed to view; second, there was no escape of gas or fecal matter into the peritoneal cavity; third, the character of the exudate was that not usually encountered in perforative peritonitis; and finally, the fluid contained no colon bacilli. We then came to the conclusion that our patient was suffering from serous peritonitis complicating typhoid fever without intestinal perforation.

REVIEW OF THE LITERATURE

Reports of cases of peritonitis complicating typhoid fever without intestinal perforation are found almost exclusively in the French literature, although Dayton,[2] Svartz and Hansen,[3] Nixon,[4] McPhedran[5] and

2. Dayton: The Relationship in Typhoid Fever Between Splenic Infarcts and Peritonitis Unassociated with Intestinal Perforation, Johns Hopkins Hospital Review, Baltimore, 1919, page 315.

3. Svartz and Hansen: Peritonite purulente diffuse sans perforation dans la fièvre typhoide, Acta Med. Scandinav. **54**:97, 1920.

4. Nixon: Enteric Fever, Peritonitis Without Perforation of the Intestine, Proc. Pathol. Soc., Dublin, 1873.

5. McPhedran: Peritoneal Effusion (Ascites) in Typhoid Fever; Paper read before Medical Society of Cleveland, 1911.

Wilson [1] have reported cases of this type. None of these cases occurred in infants, and even Wilson's case was at the upper limit of the child-age group. The textbooks on diseases of children and infants make no mention of it whatever. Jochmann,[6] in his textbook on Infectious Diseases, states that peritonitis rarely does occur without perforation. Svartz and Hansen [3] report one case in an adult, in which they believe that the peritonitis occurred by direct extension from the inflammatory lesion in the intestinal wall to the peritoneum. They also group the cases which had previously been reported in three classes, depending on the type of inflammatory fluid present in the peritoneum. Thus, of the fifty-two cases reported up to that date, one-third had a fibrinous exudate, ten a purulent exudate and the remainder a serofibrinous exudate. In only four (7.7 per cent.) of these patients, typhoid bacilli were found in the exudate, and only 25 per cent. of the entire fifty-two patients recovered. No mention is made of the agglutinative property of the exudate, as was evidenced in our case. Wilson [7] also states that peritonitis may occur through direct extension of the intestinal ulceration to the serous membrane without actual perforation.

Jochmann [6] states that when marked ulceration occurs in Peyer's patches, the typhoid bacilli may migrate through the serous coat and thus produce peritonitis. This type of peritonitis, according to Jochmann, offers a much better prognosis and does not run as stormy a course as the perforative type. He also expresses the belief that typhoid bacilli may enter the peritoneal cavity by way of a broken-down mesenteric lymph node.

Woimant [8] states that peritonitis without perforation may be caused by the migration of the organism from any viscus in the abdominal cavity, most frequently from the small intestine, appendix and mesenteric glands. According to him, the symptoms of peritonitis without perforation are exactly similar to those occurring with perforation; therefore he advises immediate laparotomy in every patient presenting manifestations of peritontitis.

Jules Roy [9] states that peritonitis without perforation complicating typhoid fever is extremely rare, and that the symptoms produced by it are very variable, the condition being produced by a migration of the organisms through the intestinal walls. The peritonitis may be local or

6. Jochmann: Lehrbuch der Infektions-Krankheiten, Berlin, J. Springer, 1914.

7. Wilson, J. C.: Keatings Cyclopedia of Diseases of Children, Philadelphia, J. B. Lippincott Company, **1**:469, 1889.

8. Woimant: Les peritonites sans perforation intestinale au cours de la fièvre typhoide, Thèse de Paris, 1911.

9. Roy, Jules: Les peritonites par propagation au cours de la fièvre typhoide, Thèse de Paris, 1907.

general, and may be masked by the intense prostration present in a severe case of typhoid fever. When the process is not generalized or develops slowly it may remain latent for a variable time.

McPhedran [5] reports a series of cases where a serous exudate only was found. All his patients recovered after laparotomy.

Dayton [2] reports a case in an adult, aged 27, in which splenic infarcts were found at necropsy. It is his belief that the typhoid bacilli found their way into the peritoneal cavity because of the coagulation necroses in the spleen. He offers this as a causative factor in this type of case, and to support his view he cites the fact that in a series of 166 cases of typhoid fever that came to necropsy at Johns Hopkins Hospital, there were three of peritonitis without perforation in which splenic infarcts were found; in the same series, however, there were seven other cases of splenic infarcts without peritonitis.

In his study of pseudoperforation during the course of typhoid fever, Blaire [10] deals principally with the differential diagnosis of true and pseudoperforation. He states that pseudoperforation presents symptoms identical with those of true perforation, except for the fact that in the former they are not so severe, and that the true perforation is often preceded by a severe intestinal hemorrhage. He believes that in peritonitis without perforation the source of the inflammation is an underlying but not perforated ulcer of the intestine. The peritonitis may remain localized or it may become generalized.

We find that there are three distinct opinions as to the causation of this condition; first, that it occurs by direct extension from the lesions in the intestines; second, that there is a migration of the organisms from some viscus in the abdominal cavity; and third, that infarcts in the spleen occur, thus paving the way for the migration of the organisms.

The fact that our patient made an uneventful recovery and improved rapidly after the laparotomy leads us to believe that neither splenic infarcts nor broken-down mesenteric glands can be considered as the predisposing factor. The fact also that no typhoid bacilli were found in the exudate makes it highly probable that in our case the peritonitis resulted from direct extension from the inflammatory lesions in the intestinal tract.

SUMMARY

A case of typhoid fever in an infant, aged 16 months, is reported, complicated by a serofibrinous peritonitis without intestinal perforation. Recovery took place after laparotomy.

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10. Blaire: Contribution a l'étude des fausses perforations de l'intestin dans la fièvre typhoide, Thèse de Paris, 1905.

PROGRESS IN PEDIATRICS

DIPHTHERIA

A REVIEW OF THE LITERATURE FOR 1923 *

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LABORATORY METHODS

An agglutination test for determining the presence of diphtheria bacilli in field (mixed) cultures has been described by Fitzgerald and Doyle.[1] The problem of differentiating true *B. diphtheriae* from diphtheroids and other morphologically similar species of micro-organisms is one of constant interest, and often of considerable difficulty to bacteriologists and public health laboratory workers. The criteria ordinarily applied in the routine examination of throat cultures are those of typical morphology and virulence. Most of the methods for doing a virulence test require the isolation of the *B. diphtheriae* in pure culture. In many cases this is difficult or impossible. To obviate this trouble, a method of testing the whole mixed culture by specific agglutination has been devised. Throat cultures to be tested are washed from Loeffler's medium with sterile physiologic sodium chlorid solution. Suitable suspensions are added to tubes containing the specific serum and incubated for two hours at 56 C. These are placed in the icebox over night and read the next day.

Of fifty-two cultures, which on smear examinations were reported positive, forty-seven gave a positive agglutination with one or both type serums in dilutions up to 1 : 640. The remaining five cultures were not agglutinated with either serum. There is a certain amount of presumptive evidence in these five cases that the agglutination reactions, which were positive though smears were negative, may have more correctly reflected the true clinical conditions. The whole procedure may be completed within twenty-four hours after the original culture is taken.

Smith [2] found that 80 strains of *B. diphtheriae* were constant in the fermentation of glucose and nonfermentation of saccharose. From

* Received for publication, Feb. 17, 1925.

1. Fitzgerald, J. G., and Doyle, D. G.: Agglutination Test for Presence of B. Diphtheriae in Field (Mixed) Cultures, J. A. M. A. **80**:1675-1677 (June 9) 1923.

2. Smith, J.: Study of Diphtheria Bacilli, with Special Reference to Their Serological Classification, J. Hygiene **22**:1-5 (Oct.) 1923.

eighty clinical cases of diphtheria, seven serologic types were isolated, but the morphology and sugar reactions do not indicate the serologic strains. Neither are virulent and avirulent strains differentiated by serologic tests.

Eagleton and Baxter [3] also find a multiplicity of serologic groups of *B. diphtheriae*. They have studied ten groups, and all but 16 of 348 strains of virulent *B. diphtheriae* could be placed in these ten groups. The technical difficulties and epidemiologic value of this work is discussed.

Powell [4] states that the virulence of different strains of *B. diphtheriae* for the guinea-pig is variable in narrow limits only. The avirulent strains do not produce toxin. Single cells of *B. diphtheriae* can be isolated easily by the Barber method, and in culture single cells of the same strain show the same virulence for guinea-pigs. During two years time, covering about fifty generations of more than 300 strains of *B. diphtheria* on Loeffler's blood serum, there was no detectable change of the virulence.

The same author found no significant morphologic changes in 299 pure line strains of *B. diphtheriae* during a period of two years. Considerable stability was also found [5] in the agglutination and absorption of agglutinin tests on single cell cultures from strains of *B. diphtheriae*. It was not possible to split a parent culture by agglutination tests.

Stovall, Scheid and Nichols [6] have found that *Staphylococcus aureus* not only kills the *B. diphtheriae* when the two are grown together, but will also change the morphology of the organisms to such an extent that they no longer fall in the same Westbrook type. Streptococci, when grown in diphtheria cultures, do not produce such changes.

Nigro [7] reports comparative bacteriologic tests with various culture mediums in sixty cases of suspected diphtheria. He found that on Pergola's serum egg yolk medium the diphtheria bacilli grew luxuriantly while other bacteria were inhibited. This is a mixture of 50 c.c. of normal blood serum (beef, horse, etc.) with one egg yolk and 0.02 gm.

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3. Eagleton, A. J., and Baxter, E. M.: Serological Classification of Bacillus Diphtheriae, J. Hygiene **22**:107-122 (Oct.) 1923.

4. Powell, H. M.: A Biological Study of Diphtheria Bacillus, Am. J. Hygiene **3**:109-120 (March) 1923.

5. Powell, H. M.: Biological Study of Diphtheria Bacillus; Property of Agglutination in Pure Line Strains Derived from Common Parent Cell, Am. J. Hygiene **3**:362-369 (July) 1923; Morphology of Pure-Line Strains, ibid., pp. 357-361.

6. Stovall, W. D.; Scheid, E., and Nichols, M. S.: Influence on Morphology and Staining of B. Diphtheriae by Growth in Mixed Cultures with Staphylococci and Streptococci, Am. J. Pub. Health **13**:748-753 (Sept.) 1923.

7. Nigro, T.: Culture Mediums for Diphtheria Bacilli, Riv. di Clin. Pediat. **21**:425-428 (July) 1923.

of potassium tellurite, with 50 c.c. of an 0.8 per cent. solution of sodium chlorid, or 50 c.c. of a 1.5 or 1.7 per cent. solution of agar.

Greenspon [8] has devised a new selective medium for the growth of diphtheria cultures as follows: To 75 c.c. of clear pig, sheep or human serum is added 1 c.c. of a 50 per cent. sodium citrate solution and sufficient dextrose veal infusion broth to bring the volume to 100 c.c. The reaction is adjusted to p_H 6.4, with a 3 per cent. citric acid solution and the medium sterilized by the fractional method. The advantages claimed are: The citric acid plays a dual rôle: (1) it inhibits the growth of the common throat organisms at the p_H 6.4, and (2) it accelerates the growth of the *B. diphtheriae*. Tests show this medium to be superior to Loeffler's serum for the cultivation and isolation of the diphtheria bacillus.

Pecori's [9] experience has been favorable with the Langer-Krüger method for differentiating diphtheria bacilli in dubious cases. It is based on the different behavior of true and false diphtheria bacilli in decolorization with alcohol after gram staining.

Lorentz [10] found that oxygen increases the production of toxin by diphtheria bacilli, and inhibits their growth. Carbon dioxid acts in the opposite way. It seems that it increases also the number of positive results of diagnostic cultures.

Bull and McKee [11] washed off the growth from a diagnostic culture with salt solution. Suitable suspensions were made, and 0.1 c.c. of this was injected into the skin on the abdomen of a guinea-pig. A similar amount was injected into a guinea-pig which had been given antitoxin. The pigs were observed for three days. The cultures which showed necrosis of the skin at the point of injection on the susceptible pig and not on the protected pig were considered to contain virulent diphtheria organisms. Of 198 strains tested, 31 gave positive reactions. Of the 31, 26 gave positive virulence tests in pure cultures. The test, thus checked against the isolation in pure culture method, gave correct results in 84 per cent. of instances. The advantages of the test are: (1) from 4 to 6 cultures can be tested on one animal, (2) the rapidity of the test, (3) elimination of isolation in pure culture, (4) results known in from forty-eight to seventy-two hours, and (5) cultures from which it is difficult to isolate the *B. diphtheriae* because of the nature of the contaminating organisms can be tested.

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8. Greenspon, E. A.: Selective Culture Medium for Diphtheria Bacillus, Bull. Johns Hopkins Hosp. **34**:30-33 (Jan.) 1923.

9. Pecori, G.: Differentiation of Diphtheria Bacilli, Policlinico (sez. prat.) **30**:553-557 (April 30) 1923.

10. Lorentz, F. H.: Changes of Bacilli in Gases, Klin. Wchnschr. **2**:206-208 (Jan. 29) 1923.

11. Bull, C. G., and McKee, C. M.: Whole-Culture Method of Testing the Virulence of Diphtheria Bacilli, Am. J. Hygiene **3**:103-108 (March) 1923.

Dernby,[12] referring to the necessity of obtaining strong toxins in order to produce effective antitoxins, outlines a new theory based on a number of experiments, on the mechanism of the formation of diphtheria toxin in cultures. The diphtheria toxin is formed mainly outside the cells. The bacilli grow, die and autolyze. In this process, proteolytic enzymes of a nature specific to these bacilli are set free. These enzymes act on the albumoses and peptones present in the bouillon. Certain of the first intermediary products are the toxic substances. The toxicity disappears if the proteolytic process is permitted to proceed further.

DIAGNOSIS

That diphtheria must be diagnosed by the clinical picture rather than by the laboratory report is emphasized by Bullowa [13] and his associates. The etiologic relationship between diphtheria and the *B. diphtheriae* has been established beyond cavil. Diphtheria is the reaction of the body to the toxins of the diphtheria bacillus. The unfortunate annual succession of tragedies witnessed at the Willard Parker Hospital, traceable to a lack of clear thinking on this point, has forced these investigators to emphasize the fact that the presence of diphtheria organisms in the throat is not synonymous with diphtheria and that the failure to find diphtheria organisms from surface throat cultures does not exclude diphtheria. The diagnosis of diphtheria should be made on the clinical picture rather than on the laboratory report.

Cultures made from the throats of 100 diphtheria patients have been investigated. When cultures are made from the surface of the exudate, the positive reports were from 80 to 86 per cent. But when a deep culture was made by placing the swab between the membrane and the tissue, the positive reports were ninety-eight from the same 100 patients. The fallacy of waiting for a report from the laboratory for a diagnosis is obvious. Cultures improperly made may be misleading and cause delay in treatment.

Delay in giving antitoxin is chargeable to two causes: (1) Parents who fail to call a competent physician. (2) Physicians who fail to read a clinical picture and thrust the burden of diagnosis on the laboratory. When in doubt concerning diphtheria, it is better to give antitoxin needlessly than to err by waiting for a laboratory report, which at best adds nothing decisive to the diagnosis.

Among eighty-two "sniffling" infants in the Goettingen University Gynecological Clinic, the nasal smear preparations never showed genuine

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12. Dernby, K. G.: Mechanism of Formation of Diphtheria Toxin, Hygiea **85**:165-181 (March 16) 1923.

13. Bullowa, J. G. M.; Hardman, R. C., and Litchfield, H. P.: Menace of Diagnostic Throat Culture in Diphtheria, J. A. M. A. **80**:240-242 (Jan. 27) 1923.

diphtheria bacilli, according to Schugt.[14] In 31 per cent., pseudodiphtheria bacilli were found; in two cases streptococci were found in pure culture, sometimes in combination with micrococci and pseudodiphtheria bacilli. Of two cases of "clinical nasal diphtheria," with slight formation of membranes, one patient showed a pure culture of streptococci, and the other showed pseudodiphtheria bacilli. Both these patients had obstinate infections with fever lasting for five and fourteen days, respectively. At the same time, two patients with genuine umbilical diphtheria were observed in the clinic. Otherwise, there were no bacilli carriers among the patients and attendants.

Schugt concludes that infection of the new-born with diphtheria bacilli from the maternal vagina does not play so considerable a part as is thought by some observers. The pseudodiphtheria bacillus may exhibit pathogenic properties in certain cases. The significance of the pus producing agents for the nasal infections of infants, especially "nasal diphtheria" is strongly emphasized by the author. For the treatment of streptococcus rhinitis, the instillation of Rivanol 1:1,000, one drop several times daily, is recommended, although the number of observations is still too small to permit any definite verdict as to results. Mixed or secondary infections are very common in so-called nasal diphtheria of infants, and probably play an important part from the clinical and therapeutic point of view, namely, the success or failure of serum treatment. Since diphtheria bacilli are known to exhibit destructive pathogenic properties, no matter what the conditions, these germs should always be looked for, especially in obstinate cases of infantile coryza associated with a purulent discharge.

Chevalley[15] calls attention to the possibility of diphtheria when an infant has rhinitis, or ulcerating cutaneous lesions at the navel or behind the ear. Such conditions are comparatively harmless. The rhinitis of inherited syphilis seems to be a favorite point of attack for the diphtheria bacillus. Virulence tests on animals seem to be the only means to exclude pseudodiphtheria bacilli in these cases.

Iams[16] states that the old textbook picture of nasal diphtheria as rare and very serious has led to wrong conclusions of the frequency of mild and often overlooked nasal cases. It is true that many of the nasal cases are toxic and the prognosis grave, but those are usually in the neglected patients, in whom there has been extensive spread of the membrane with a profuse nasal discharge, and where there is no doubt as to the diagnosis.

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14. Schugt, P.: Diphtheria of Nose in Infants, München. med. Wchnschr. **70**:598-600 (May 11) 1923.
15. Chevalley, M.: Diphtheria in Infants, Nourrisson **11**:33-45 (Jan.) 1923.
16. Iams, J. D.: Nasal Diphtheria, Atlantic M. J. **26**:448-451 (April) 1923.

The nose has been neglected often in routine cultures. In the Pittsburgh schools in 1921 and 1922, 13,841 throat cultures were taken, 200, or 1.44 per cent. of which were positive. During the same period 696 nasal cultures were made with 60, or 8.6 per cent., positive. Had more nasal cultures been made, it is probable that more positive cultures would have been found.

Regarding the mortality from nasal diphtheria, the records of 911 patients with nasal diphtheria in the Pittsburgh Municipal Hospital during the last ten years show a mortality of 2.78 per cent., against a general mortality of 5 per cent. for all diphtheria cases.

The medical profession has gradually awakened to the importance of throat cultures and early antitoxin in faucial cases of diphtheria. If more nose cultures were made, it is believed that many carriers and patients with mild attacks would be found and treated. Citing some forty cases from his practice, Iams illustrates this point: fifteen, or 37.5 per cent. of these had positive nasal cultures.

His conclusions are as follows:

1. Nasal cultures should be made on as large a scale as throat cultures.
2. Primary diphtheria of the nose is not infrequent.
3. Excepting the late neglected cases, the toxicity of the nasal type is not so high as other types.
4. All cases of rhinitis, particularly if unilateral, should be cultured.
5. The nasal variety of carrier is an important factor in prolonging the epidemic.

Göppert[17] points out that a positive bacteriologic finding does not prove that the child is suffering from diphtheria, and that negative findings do not disprove it. The most important sign is the typical membrane, though it may be due to other infections. Sanguinolent secretion is important, but not very common. Some cases are chronic. Unilateral atrophic rhinitis is especially under suspicion as being of a diphtheritic origin.

In the German literature, several articles on wound diphtheria appear. Landau[18] examined 170 wounds for diphtheria bacilli. He found bacilli resembling diphtheria in 18.2 per cent. Most were so characteristic that a mere examination of similar bacilli from the throat would have led to the diagnosis of "diphtheria." A complete examination, however, showed that not one of these strains was typical. Diphtheroid

17. Göppert, F.: Nasal Diptheria, Monatschr. f. Kinderh. **25**:201-210 (March) 1923.

18. Landau, H.: Diagnosis and Treatment of Wound Diphtheria, Klin. Wchnschr. **2**:595-597 (March 26) 1923.

bacilli are very common in wounds and Loeffler's medium alone is not sufficient for differentiation in these cases.

Other articles on the same subject are contributed by Grossmann and Radice,[19] Rieder,[20] Elfeldt and Donges,[21] and Landau.[22] Uhlhorn [23] insists on the importance of early recognition and antitoxin treatment of diphtheria infection of a wound, as the diphtheria is apt to entail post-diphtheritic paralysis, besides the danger of infecting others. If bacteriologic examination gives dubious findings, inoculation of animals should not be omitted.

Baldwin, McCallum and Doull [24] describe an interesting case. A young physician accidentally pricked his hand while doing a virulence test with diphtheria organisms on a guinea-pig. A typical necrotic ulcer appeared on both the physician and the guinea-pig. During the night the physician removed the bandage from the hand, and he thinks he put his thumb in his mouth. In a few days a membrane appeared in the throat. Both the thumb and pharynx yielded readily to antitoxin treatment.

Blau [25] gives as the diagnostic points in pharyngeal diphtheria, a quiescent onset, with a low fever, sore throat and a continuous exudate in the throat. It is most often confused with tonsillitis which usually has a sudden onset, high fever, prostration and a patchy exudate. With antitoxin the symptoms of the former abate, while the latter symptoms continue in spite of all treatment. A chronic, serosanguinous nasal discharge in a child is always suspected, and cultures for diphtheria should be made. A membrane is usually not seen in nasal diphtheria. Laryngeal diphtheria is often confused with catarrhal croup. The onset with hoarseness, croupy cough, stridor, dyspnea and fever is similar in both. But in membranous croup the child is often more prostrated, the symptoms grow continually worse with no periods of remission and the fever is usually low. Dyspnea, chest recession with cyanosis rapidly appear and continue, while in croup these are usually present only in moderation during the paroxysms. In all suspicious cases, diphtheria cultures should be made. In the pharyngeal and nasal types the *B.*

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19. Grossmann, W., and Radice, L.: Wound Diphtheria, Klin. Wchnschr. **2**:2126-2128 (Nov. 12) 1923.

20. Rieder, W.: Diagnosis of Wound Diphtheria, Beitr. z. Klin. Chir. **129**: 296-299, 1923.

21. Elfeldt and Donges: Wound Diphtheria at Rostock, Beitr. z. Klin. Chir. **128**:562-579, 1923.

22. Landau, H.: Wound Diphtheria, Arch. f. Klin. Chir. **123**:716-757, 1923.

23. Uhlhorn, C.: Wound Diphtheria, Arch. f. Klin. Chir. **123**:833-841, 1923.

24. Baldwin, A. H.; McCallum, F., and Doull, J. A.: Case of Pharyngeal Diphtheria Probably Due to Auto-Infection from Diphtheric Lesion of Thumb, J. A. M. A. **80**:1375 (May 12) 1923.

25. Blau, A. I.: Diagnostic Points in Diphtheria, New York M. J. **117**:275-276 (March 7) 1923.

diphtheria is usually found. In the laryngeal type, cultures may be negative even in advanced cases due to the inaccessibility of the membrane.

According to Dupuy,[26] very little has been said or written about that anatomic type of diphtheria which begins in the lower respiratory tract. Tracheobronchial diphtheria may be mistaken for bronchopneumonia or capillary bronchitis. When the invasion begins in the lower air tract, cultures taken from the throat will of necessity be negative. The most suspicious sign is the gradual onset of a persistent and progressive dyspnea, which increases to such a degree that there is sinking in of the suprasternal and diaphragmatic regions. At first breathing is wheezy and noisy. Inspiratory stridor soon manifests itself and dominates the symptom complex. There is a croupy cough, but the voice is clear and unaltered. On account of "air hunger," the patient requires frequent change of posture. Toxemia is reflected in the rapid heart action and rise of temperature. The dominant signal of distress is the mechanical obstruction to breathing.

COMPLICATIONS

Loth [27] studied both clinically and pathologically seventeen patients, fatally ill of diphtheria, from the New Haven Hospital. The average age of the patients was 3.6 years, except in one. The average days of illness on admission to the hospital was 5.8, and the average duration of the illness was 10.8 days. Myocarditis was an antemortem diagnosis in three of the seventeen patients. Cardiac enlargement was noted in four, and three showed arrhythmia. The gross pathologic findings showed dilatation of the heart to the right in seven patients, bronchopneumonia in sixteen, fibrinous pleurisy in six and acute cervical lymphadenitis in three of the seventeen. Microscopic examinations of sections from the heart showed some cloudy swelling, fat accumulation and a slight increase in interstitial cells. A definite inflammatory reaction (true myocarditis) is rarely seen (one of nineteen patients studied). The myocardial changes are not more pronounced than those found in other acute infectious diseases. Lethal injections of diphtheria toxin into guinea-pigs produced changes in heart muscle similar to those in the human heart in fatal diphtheria, but such injections did not cause a true inflammatory reaction.

Blacher [28] finds increased irritability and fatigue of the whole neuromuscular cardiac apparatus in diphtheria. In the first two or three

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26. Dupuy, H.: Tracheobronchial Diphtheria, New Orleans M. & S. J. **76**:113-115 (Sept.) 1923.

27. Loth, M.: Clinical and Pathologic Study of the Heart in Diphtheria, Arch. Int. Med. **31**:637-652 (May) 1923.

28. Blacher, W.: Rôle of Nervous System in Heart Disturbances in Diphtheria, Jahrb. f. Kinderh. **101**:13-80 (Feb.) 1923.

weeks progressive vagotonia is evident. Fatigue of the vagus nerve becomes more apparent after this stage, and may be accompanied by irritability of the accelerans. Nevertheless, the irritability of the pneumogastric may appear even in this stage, especially in attacks following small exogenous and endogenous stimuli. This lowering of the threshold of stimulation of the vagus and accelerans is the reason why cardiac stimulants should be used with great care in diphtheria.

According to statistical data, Cramer [29] finds the frequency of paralysis in diphtheria varies between 11 and 20 per cent. in the cases of Loeffler bacillus infection. The virulence of the bacillus is undoubtedly chiefly responsible for the frequency of diphtheritic paralysis. The greatest number of the patients observed are above the age of 10 years, indicating that adult patients are apparently more likely to show paralysis than children. Some writers believe that the frequency of diphtheritic paralysis has not diminished since the employment of antidiphtheritic serotherapy, and a few actually believe that this medication has increased the incidence. This apparently paradoxical fact is readily understood when it is kept in mind that, since the introduction of serotherapy, a greater number of patients recover and go through the period of convalescence, during which time paralysis develops. It is usually admitted that early paralysis of the palate has a bad prognosis, leading to death in 60 per cent. of the patients. On the other hand, the prognosis in the patients with late paralysis, especially when the paralysis remains localized in the throat, is good. A bad prognosis must be rendered only in those patients in whom it becomes generalized and involves the respiratory muscles, more particularly the diaphragm.

Cowie [30] cites a typical case of diphtheritic paralysis. A girl, aged 9 years, came to the clinic, complaining of inability to stand and walk normally. The external rectus muscle on the left side seemed deficient, and the eye turned inward. She had a diplopia. The child had become ill with a sore throat five weeks before. Her physician suspected diphtheria, a culture was taken and antitoxin was given the following morning. About that time the child regurgitated through the nose. The history would lead one to believe that the condition cleared up. She made a good recovery, went about her play and school work until the fifth week after the infection, when convalescence paralysis developed. Nasal palsy is a characteristic of the early paralysis. This case illustrates the necessity of the physician explaining the disease to the patient's parents in such a way that they can understand it, and also the desirability of a family maintaining faith in their physician. The family physician in

29. Cramer, A.: Present Status of Diphtheric Paralysis, Rev. méd. de la Suisse Rom. **43**:98-106 (Feb.) 1923.

30. Cowie, D. M.: M. Clin. N. Am. **6**:1297-1300 (March) 1923.

this case told the parents that the condition would take care of itself and that everything would be all right, but apparently he did not have time or take time to explain that it might be two or three months before all the paralyses would clear up. Becoming impatient, the parents called a second physician who told them that this convalescence paralysis was due to too much antitoxin. The late palsy may possibly have been due to an insufficient amount of antitoxin having been administered rather than too much. A guarded prognosis should be made in diphtheria, and the family should be instructed to report any aches or any disturbance in walking.

Zoeller[31] affirms that the earlier in diphtheria the antitoxin is injected, the less the proportion of cases with paralysis. When the paralysis is once developed, antitoxin should be given freely for three to five days. Comby has reported rapid cures under this treatment in thirteen patients. Massive doses should be given in early diphtheritic paralysis. With tardy paralysis, it should also be given if not administered before. If it does no good, at least it does no harm. Sometimes small doses answer the purpose. Ginestous witnessed the subsidence of a paralysis of accommodation, which had persisted for two years, when two injections of 10 c.c. of antitoxin were given. If the patient is a carrier, antitoxin is required, as the bacilli continue to secrete toxin. No tendency to paralysis has ever been noted in healthy subjects or in animals which were given diphtheria antitoxin.

To determine whether a meningeal reaction occurs in the spinal fluid in postdiphtheritic paralysis, and to assist in establishing a cytologic and chemical formula for the fluid in this disease, which may be of importance in a differential diagnosis, a study of this subject was undertaken by Regan, Regan and Wilson.[32] The spinal fluid in postdiphtheritic paralysis has received scant attention in this country. This fluid may be important in the differential diagnosis between obscure cases of postdiphtheritic paralysis and anterior poliomyelitis; other conditions such as capillary bronchitis, epidemic encephalitis, tabes dorsalis and multiple neuritis, may at times simulate a postdiphtheritic paralysis.

A series of 28 specimens of spinal fluid from sixteen patients were examined by Regan and his associates at various intervals from the second day to the eleventh week of the paralysis. Nearly two-thirds of the patients had a generalized paralysis and five died. All followed a moderate or severe initial angina, commonly of a polymicrobian or septic

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31. Zoeller, C.: Present Status of Diphtheric Paralysis, Rev. de méd. **40**: 86-103 (Feb.) 1923; ibid. **40**:157-181 (March) 1923.

32. Regan, J. C.; Regan, C., and Wilson, B.: Characteristics of Cerebrospinal Fluid in Postdiphtheric Paralysis, Am. J. Dis. Child. **25**:284-289 (April) 1923.

form, with extensive membrane formation which was frequently accompanied by myocarditis.

The conclusions are:

1. The cerebrospinal fluid in postdiphtheritic paralysis was clear, limpid, under normal or slightly increased pressure.

2. The Bordet-Wassermann reaction was uniformly negative.

3. The cell count was always below 10 per c.mm., small lymphocytes predominating.

4. The globulin was increased in less than one-third of the patients and never marked.

5. The colloidal gold reaction showed reduction usually in the first five or six dilutions. This reaction subsided gradually with convalescence, and was the most constant pathologic reaction noted in the series.

Glesinger-Reischer and Glesinger [33] found a moderate increase in blood urea in three-fourths of their twenty-one patients. Antitoxin injections were followed by a decrease in the blood urea in diphtheria, but not in four patients with tonsillitis of other origin.

The association of scarlet fever and diphtheria is of interest, and has been investigated more particularly from the standpoint of postscarlatinal diphtheria. R. T. Grant [34] discusses the finding of diphtheria-like bacilli in the acute stage of scarlet fever and the effect of this association on the patient. Routine examinations of aural discharges in cases of scarlet fever have shown a diphtheria-like organism frequently; most of these are of the nonvirulent type. Nose cultures vary from 8.6 to 12.7 per cent. The majority of these are also nonvirulent, but true virulent types are found in the nose more frequently than in the ears. On admission, routine throat cultures vary from 1.2 to 5.8 per cent. for diphtheria-like organisms and higher percentages in later cultures.

This series covers 14,770 scarlet fever patients over a ten-year period. During the first four years, only those throats showing a membranous angina were cultured. In 6,180 patients, diphtheria-like bacilli were present in seventy-one, or in 1.1 per cent.

During the transition year, the average in 2,455 patients was 1.3 per cent. During the last five years routine throat cultures were made on all patients with scarlet fever admitted to hospital. In 6,132 patients diphtheria-like bacilli were found 180 times, or in 2.9 per cent. The yearly average varied from 1.4 per cent. to 3.6 per cent. and seemed to

33. Glesinger-Reischer, G., and Glesinger, B.: Urea in Blood in Diphtheria and Its Changes in Specific Treatment, Wien. klin. Wchnschr. **36**:181-183 (March 8) 1923.

34. Grant, R. T.: Diphtherial Infection in Scarlet Fever, J. Hygiene **21**:250-257 (May) 1923.

follow the incidence of diphtheria outside of the hospital. Some of these represented patients with scarlet fever who were diphtheria carriers. These usually progressed favorably, the mortality being only 1.3 per cent. The other type, with true diphtheria and scarlet fever, were acutely ill and had a mortality of 24 per cent.

It has been stated that where the two diseases occur in the same patient, diphtheria usually follows scarlet fever. In this series the reverse was true. The incidence of postdiphtheritic scarlet fever was over 3 per cent., as compared to 1.3 per cent. for postscarlatinal diphtheria.

Van Saum [35] reports a case of diphtheritic vaginitis in a girl, aged 6 years. The organism persisted in the vaginal tract for forty-two days and in the nose for five months. The child had perhaps been a nasal carrier for some time. Over the vulva there was an extensive membrane. The patient responded to antitoxin treatment slowly, but had no paralysis.

A search of the literature for thirty years yields reports of only twenty-six patients with diphtheritic vaginitis, and few of these were confirmed by bacteriologic methods. Primary diphtheria of the genitals in children is apparently rare.

De Rudder [36] describes a case of paralytic ileus occurring in an infant, aged 3 months, fourteen days after nasal diphtheria.

Brisotto [37] discusses the special character of the diphtheria bacillus in certain forms of sinusitis. In two cases of inflammatory infections of the accessory nasal sinuses, in adult patients (a man, aged 27, and a woman, aged 55), he found in the pus a bacillus which—while its biologic characteristics exactly corresponded to those of the diphtheria bacillus, especially with respect to its virulence and the changes produced in the guinea-pig, identical with those usually produced by the Loeffler bacillus—nevertheless may appear under certain conditions as a strictly anaerobic organism. This bacillus, immediately after its isolation presents ramifying forms, which were observed in some cultures from both patients, as well as very long filament-like forms noted in the second patient, always in anaerobic cultures.

A virulence test shows that this organism is *B. diphtheriae.* A further differential sign between the Loeffler bacillus and the pseudo-diphtheritic bacillus is the ability of the former, in more or less virulent strains, to grow under anaerobic conditions, while the latter grows

35. Van Saum, A. I.: Diphtheric Vaginitis in Children, J. Infect. Dis. **33**: 124-129 (Aug.) 1923.

36. De Rudder, B.: Paralytic Ileus After Nasal Diphtheria, Klin. Wchnschr. **2**:23 (Jan. 1) 1923.

37. Brisotto, P.: Special Character of the Diphtheria Bacillus in Certain Forms of Sinusitis, Riforma med. **39**:290-296 (March 26) 1923.

strictly aerobically. The organisms isolated from these cases grow anaerobically. Both patients suffered from maxillary sinus disease, and both recovered after operation.

Kawano's [38] bacteriologic findings and experiments gave no indication of any causal connection between ozena and diphtheria. The bacilli found in 12 per cent. of his patients were only of the pseudodiphtheritic type.

Jacobs [39] reports a case of dry gangrene, requiring the amputation of both legs, due to thrombosis of the popliteal artery in a girl, aged 8 years, about six weeks after a severe attack of pharyngeal diphtheria. Cultures from the popliteal artery were negative.

Sumner [40] reports the death from anaphylactic shock of a girl, aged 8 years, in a few minutes following a prophylactic injection of 1,000 units of diphtheria antitoxin. A number of other contacts were injected at the same time with the same antitoxin with no untoward results. This patient had a history of asthma and a hypersensitiveness to horse emanations. Anaphylactic shock after first injections is rare. Estimates place the mortality at 1 : 1,000,000 for the first injection, and 1 : 10,000 for the second. These deaths, though appallingly sudden and regrettable, merge into insignificance when one reflects on the great saving of life by serum injections, for example, tetanus in the World War and diphtheria in civil life. The risk is less than the most trivial surgical operation.

CARRIERS

McGuire and Hitchens [41] made throat cultures from 1,080 applicants at the Citizen's Military Training Camp at Camp Meade. Of these, eighty-three were suspicious for *B. diphtheriae* and sixty-six were tested for virulence; nine were found to contain virulent organisms. This meant a carrier rate of 0.83 per cent., or almost 1 per cent. among healthy young men between the ages of 17 and 21. Park and Beebe, in an earlier survey, found a carrier rate of 2.4 per cent. on 330 healthy persons. Schick tests on seven of these carriers in McGuire and Hitchens' series showed three positive and four negative reactions. Schick tests on 883 of the students enrolled gave 453, or 55 per cent., positive reactions. As further observations are made in these training camps, much valuable epidemiologic information may be had for all infectious diseases.

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38. Kawano, R.: Diphtheria and Atrophic Rhinitis, Wien. klin. Wchnschr. **36**:737-739 (Oct. 18) 1923.

39. Jacobs, A. G.: Diphtheria with Unusual Complications, South. M. J. **16**:602-605 (Aug.) 1923.

40. Sumner, F. W.: Sudden Death from Anaphylactic Shock Following Antitoxin, Brit. M. J. **1**:465-466 (March 17) 1923.

41. McGuire, P. F., and Hitchens, A. P.: Epidemiologic Survey in a Citizen's Military Training Camp, J. A. M. A. **80**:665-670 (March 10) 1923.

The statistics presented by Schlayer [42] cover the period from August, 1914, to March, 1918, and include only the German troops and not the enemy prisoners in Germany. Among German field troops for the four years of war, according to the hospital sick reports, there were 21,862 patients with diphtheria with 479 deaths. Among German garrison troops there were 26,461 patients with 535 deaths. The percentage of fatalities gradually decreased in both the garrison and field armies during the four years of the war, reaching the highest point in the first year and the lowest point in the fourth year of the war. The statistics prove that diphtheria does not belong to the class of diseases which exhibit a noticeable increase in frequency during conditions incident to war, such as typhoid and dysentery do. It should not, therefore, be classed among the diseases due to war conditions.

The number of healthy carriers in comparison with the number of those sick with the disease was always high in all epidemics: sixty-two carriers in an epidemic of ninety-five patients; thirty-nine carriers and thirteen patients; thirty-two carriers and eighteen sick; thirty carriers and fourteen patients. Schlayer feels that this factor in the spread of diphtheria deserves particular attention in the fight against the disease.

1. In an attempt to clear up carriers, iodin was used most often, either in the form of the tincture alone or after a preliminary application of some remedy like ammonium carbonate to remove the mucus. A mixture of some iodin preparation (potassium iodid, 5 per cent., and a few drops of hydrochloric acid) was often tried with hydrogen peroxid gargle, in order that the free iodin might work on the mucous membranes in its nascent state. The results varied: (*a*) permanent cure in from eight to ten days of twenty-five carriers, (*b*) thirteen cured "in a few days," (*c*) 18 per cent. of forty-four carriers not cured.

2. Lomry suggests a 4 per cent. watery or glycerin-iodin-potassium iodid solution (stock solution: iodin 10, potassium iodid, 15, distilled water, 100) or "a more potent one" of 4 c.c. of the stock solution to 100 c.c. sheep blood serum, freshly mixed, and slowly injected into each nostril and the throat (twice daily) with a long-necked syringe in doses of from 20 to 25 c.c. Bacilli are supposed to have disappeared in from five to six days, but reports vary. Complaints and pain, however, always accompanied the treatment, though it appeared to be more effective than the plain iodin swab.

3. Other treatments used included the employment of tribrom-betanaphtol by simple swabbing (Leschke), and solutions of mercuric oxycyanate 1:4,000, used on sixteen carriers with excellent results by Justitz. Pfeiffer reports work with eukupin, swabbing with a 1 to 2

42. Schlayer, C.: Diphtheria and the War, Mil. Surgeon **52**:261-272 (March) 1923.

per cent. solution of eukupin, atomizing with a weaker solution (from 0.1 to .03:10), etc. Schlayer has used this in the form of a throat swab in a 2 per cent. solution in some obstinate cases which had resisted other methods of treatment for long periods with fairly rapid results, but he has also had many failures. If applied too frequently, eukupin may produce superficial blisters.

4. Iodo-sulphon-oxybenzolpyridine, used by Bischoff and Kausch, has not been used to any great extent.

5. Rolly tries to obtain an acute inflammation of the throat by the use of ultraviolet rays from the sun, and hopes to kill the bacteria in the same manner in which they are destroyed in the bowels by the same means.

6. Wittmaack has not obtained decided results in use of local applications of diphtheria serums in dry form, nor with the local injections of serum, nor in subcutaneous or intramuscular serum injections.

Sumner [43] gives his experience in a school of 200 boys at Simla, India, where there were 15 patients with diphtheria from March 14 to July 7, 1922. The original patient was a recent arrival. The others were direct contact patients, and the interest of the whole epidemic centers in carriers both "healthy" and "diseased." By "healthy" is meant those who have not had the disease but who harbor diphtheria bacilli in the throat; by "diseased" is meant those who have had diphtheria and still carry the organisms after convalescence.

When the first boy became ill, the whole 200 boys were given a prophylactic injection of diphtheria antitoxin. About 5 per cent. of these developed a mild serum reaction. As boys later developed diphtheria, contacts were given additional prophylactic injections. About 10 per cent. of these showed mild anaphylactic reactions (rashes and joint pains).

There were eight patients in March, following the original one. From May 19 to July 7 there were seven additional sporadic subjects. Examination of the throats of the original patients by cultures on three successive days showed one to be an intermittent carrier. Later cultures in July from these boys, by swabs on six successive days, showed that six of the eight were intermittent carriers. These were isolated. Two months later another sporadic case occurred. It was then decided to examine the throats of all the boys and the menial help in the school, and to make cultures from all who showed enlarged tonsils or reddened throats. There were fifty-nine of these. One was a mild ambulatory case of diphtheria, and 50 per cent. of the remaining fifty-eight were carriers of diphtheria bacilli. Prophylaxis thus appears to be a two-

43. Sumner, F. W.: Diphtheria Carriers, Brit. M. J. 1:808 (May 12) 1923.

edged sword. Prophylactic injections of antitoxin may be given to all contacts; but if antitoxin only is used, we may expect a crop of diphtheria carriers. These must be searched out and eliminated if the outbreak is to be controlled.

In an investigation, reported by Culverwell and Forbes,[44] of a small outbreak of diphtheria at an industrial school in the Midlands, in England, it was found that a certain boy had nasal excoriation which yielded, on swabbing and cultivation, abundant *B. diphtheriae,* and he had been transferred to a hospital.

The tooth brushes belonging to the boys were each clearly marked with the owner's number, and when not required were hung separately by means of rings from a shelf in the school lavatory. "Carbolic" tooth powder was in general use and was supplied to the boys from a common bowl. After the boy's removal to the hospital, his toothbrush and also brushes of other boys were soaked for thirty-six hours in a 5 per cent. solution of a disinfectant of the lysol class. For about ten days between this soaking and its removal for bacteriologic examination, the brush hung in its usual place in the school lavatory. About a score of bristles were detached and cultivated on the surface of plated blood serum. On culture and animal tests, the organisms present were found to be indisputably virulent *B. diphtheriae.*

There is no doubt that a toothbrush may harbor infection and may lead to dissemination of infection from an active diphtheria carrier. The use in common of a tooth powder bowl may also be responsible. The practical disinfection of toothbrushes, either by powder or by immersion in a reputed "disinfectant," is not as reliable as commonly believed, according to results obtained by Culverwell and Forbes in a test of three used toothbrushes, artificially infected and then soaked in lysol. These brushes still contained virulent diphtheria bacilli. The safest course is to destroy the toothbrush.

Litterer [45] reports the finding of virulent *B. diphtheriae* in the throats of ten fowls suffering from roup. The chickens responded to antitoxin treatment when given early. Litterer's conclusions are: (1) This is the first instance so far as the author has been able to find in literature, in which virulent Klebs-Loeffler bacilli have been isolated from fowls; (2) it is probable that the fowls received their infection from human beings harboring virulent bacilli, since persistent virulent carriers were demonstrated in the families that owned the fowls; (3) experiments on healthy fowls failed to produce a permanent carrier state. Certainly

44. Culverwell, G. H., and Forbes, J. G.: The Toothbrush as a Carrier of Virulent Diphtheria Bacilli, Lancet **2**:255-257 (Aug. 4) 1923.

45. Litterer, W.: Virulent Diphtheria Bacilli Isolated from Chickens Suffering from Roup, South. M. J. **16**:514-518 (July) 1923.

nothing corresponding to carriers as seen in man was observed. Negative results were also obtained in two fowls suffering with roup; (4) the demonstration of virulent Klebs-Loeffler bacilli in fowls opens up a new field for the means of dissemination of the Klebs-Loeffler bacilli among human beings.

PREVENTION

The literature on the Schick test and toxin-antitoxin immunization against diphtheria is voluminous. To cover all of this is impossible in a brief review; only the outstanding articles will be included.

Park [46] defines the Schick test as the local effect of the intracutaneous injection of $\frac{1}{40}$ of a minimum fatal dose of diphtheria toxin in 0.2 c.c. of physiologic sodium chlorid solution. It is a dependable test if the correct amount of toxin is given strictly intracutaneously. Emphasis is laid first, on a carefully standardized toxin accurately diluted; next, the injection must be intracutaneous. If the technic of administration is faulty, then the results are misleading. Probably some of the discrediting results of the test have been due to these two factors. Summing up: a negative or wholly pseudoreaction read on the third or fourth day is reliable indication of present and future immunity to diphtheria, provided a standard toxin is used, and the technic is not faulty.

The value of the control test is twofold; in the first place, it helps to point out those hypersensitive persons who are apt to have more severe reactions with the toxin-antitoxin mixture; in the second place it is helpful in deciding whether a doubtful Schick reaction is due to the toxin or to the foreign protein in the toxin broth. In about 5 per cent. of the Schick tests there is considerable doubt as to whether a pseudoreaction (protein) or a combined reaction (toxin and protein) is present. If the toxin and the control reaction is exactly the same, it is pretty safe to assume that the Schick test is a pseudoreaction due to the proteins mixed with the toxin. On the other hand, if there is no reaction with the heated toxin, it is safe to assume that the reaction in the Schick test was due to the toxin. The control test is advocated for children over 6 years of age. If one does not fear severe reactions, and there are comparatively few in young children, and promise to become fewer with the 0.1 L + dose of toxin-antitoxin mixture, and does not mind immunizing the extra 5 per cent. of the patients who might be eliminated by the heated toxin injection, the control test may safely be eliminated.

Does a negative Schick test give assurance that sufficient antitoxin is present to protect against diphtheria? Schick attempted to select that amount of toxin for the intracutaneous test which, if it gave a reaction, indicated that the patient was not immune because of antitoxin; if no

46. Park, W. H.: Use of Schick Test and of Toxin-Antitoxin Injections in Prevention of Diphtheria, New York State J. M. **23**:1-6 (Jan.) 1923.

reaction developed, that the patient was immune. To select an amount of toxin which would so separate patients under all conditions is too much to expect. Antitoxin which would just prevent diphtheria under conditions of health would hardly do so if the condition were complicated, for example, by measles or tonsillitis. Park is convinced that there are patients with a slight tonsillar exudate and positive cultures who give a negative Schick test. If a diphtheria carrier contracts tonsillitis, he may show a slight exudate and the condition be called diphtheria. From his considerable experience, Park states that it is possible for a few such patients to have a mild attack of diphtheria, even though they have a negative Schick reaction, but he believes the attack will never be severe and that the patients will quickly recover without antitoxin.

The use of isolation of carriers and immunizing doses of antitoxin has caused a moderate decrease in diphtheria in a few localities. The use of antitoxin has reduced the mortality to one-fifth that of previous days. But in New York state outside of the city the mortality has risen from 11 to 18 per hundred thousand. In New York City it has risen from 19 per hundred thousand in 1916 to 22 per hundred thousand in 1919. Up to 1920 in New York City, about 15,000 cases and 1,200 deaths occurred annually. These facts indicate that we have not yet conquered diphtheria.

After experiments showed that toxin-antitoxin mixtures were safe and that they produced an active immunity over a period of years, an attempt was made to test the school children of New York City by means of the Schick reaction, and to protect those giving a positive reaction by toxin-antitoxin injections during 1920 and 1921. The 3 L + dose of toxin-antitoxin was used originally. Later it was found that a mixture containing 0.1 L + dose of toxin per cubic centimeter gives approximately the same degree of immunity less the somewhat annoying reactions of the stronger mixture.

Approximately 80 per cent. of those with a positive Schick reaction become negative from three to six months after a course of three injections of the toxin-antitoxin mixtures. Of those receiving only 2 injections, about 70 per cent., and of those receiving 1 injection, about 50 per cent. gave a negative reaction from three to six months later by means of the Schick test.

One hundred and eighty thousand school children were observed. In 90,000 children tested and treated, twelve cases of probable diphtheria developed. In 90,000 children untested and untreated, there were fifty-four cases of diphtheria. In other words, there was four and one-half times as much diphtheria occurring among the untreated as among the treated children. It is further observed that during the last six months (article published, January, 1923), in New York City there have been

less cases and deaths from diphtheria than ever recorded before. For the first time, the death rate for diphtheria in New York City is lower than that for the state outside of the city.

Zingher [47] considers the proper dilutions of toxin one of the most important elements in the accuracy of the Schick test. When large numbers of children are to be tested, the use of unheated bulk toxin for the Schick test and of heated bulk toxin for the control is recommended as the most accurate and economical method of carrying on the work. The Schick test was made on the right forearm of each child and the control test with heated toxin on the left forearm. The reactions were read from the third to the seventh day after the test, the day of reading depending on how the work could be arranged in the schools.

On 151,261 children, aged from 5 to 17 years, there were 101,446 negative and 49,815 positive (or 32.9 per cent.) Schick reactions in public and parochial schools in Manhattan and the Bronx. Zingher's summary is as follows:

1. More than 150,000 children have been given the Schick test during the last two years in the public and parochial schools of the boroughs of Manhattan and the Bronx.

2. A high percentage of positive Schick reactions is found among the children in the entering classes in the kindergarten and 1 A grades. This varies in different schools from 60 to 85 per cent. The toxin-antitoxin injections could, therefore, be given to these young children without preliminary Schick tests.

3. The schools located in the less congested sections of the city and attended by children of the more well-to-do show, as a rule, from 100 to 200 per cent. more Schick positive reactors than those located in the crowded parts and attended by children of the poorer classes.

4. Repeated exposure to infection with the diphtheria bacillus is probably the most important factor in the development of "natural" immunity to this disease. Racial and hereditary family factors, although less important, also play a rôle.

5. Girls show a somewhat larger percentage of positive Schick reactions than boys. They also show more negative-pseudo and positive combined reactions. This holds true also for adults.

6. The high percentage of positive Schick reactors among young children of preschool age may, under certain conditions, render it advisable to simplify the procedure of immunization by omitting the preliminary Schick test. The children are simply injected with three doses of toxin-antitoxin. Under these circumstances, however, the children should not be pronounced immune to diphtheria until a supplementary Schick test, performed six months later, proves negative.

7. Diphtheria is the foremost fatal disease in children from 3 to 5 years of age, and ranks third among the fatal diseases of children from 1 to 3 years of age. Only diarrhea and pneumonia precede diphtheria in the mortality tables. The dangerous laryngeal form occurs in the young children. It is for these reasons that physicians should urge parents to take advantage of these newer methods to protect their young children against diphtheria. In fact, active immunization against diphtheria should become as much of a routine for all children between 6 months and 6 years as vaccination is against smallpox today.

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47. Zingher, A.: Schick Test Performed on More Than 150,000 Children in Public and Parochial Schools in New York (Manhattan and the Bronx), Am. J. Dis. Child. **25**:392-405 (May) 1923.

McClelland [48] summarizes his experience with Schick test in the Cleveland schools as follows:

1. Schick tests have been done on 6,893 children, mostly in the kindergarten and first grade; 4,307, or 62.5 per cent., gave positive reactions.

2. In order to simplify the work, the control tests were omitted in these young children.

3. Children from congested districts were found immune in higher percentage than those from noncongested districts.

4. Susceptibility, as shown by positive Schick tests in children, aged 5 and 6 years, was found considerably higher than former reports would indicate. In our experience from 50 to 85 per cent. show positive reactions.

Boudreau [49] reviews the successes of preventive medicine in combating smallpox, typhoid fever and yellow fever, and states that diphtheria can similarly be prevented if the public is taught the value and means of prevention. The Schick test and toxin-antitoxin can accomplish this, but the public must be told that neglect of this constitutes criminal negligence. In Ohio there is an average of 500 deaths, and from 5,000 to 10,000 cases of diphtheria each year. The annual financial loss is probably in excess of $5,000,000. The mortality and morbidity from diphtheria could be cut down to one-half to one-third of its present rate within a year if every health commissioner in Ohio were to carry out a program of education and immunization intelligently and persistently. This is a new but not an untried weapon and, if used, can materially reduce diphtheria.

Vogel [50] has seen many cases of diphtheria in recent years, and has recently applied extensive prophylactic injections of diphtheria toxin-antitoxin. Altogether, 405 persons were injected, 252 receiving one injection, 132 receiving two injections and twenty receiving three injections. The disturbances associated with the injections, such as stiffness of the injected arm and fever, were generally inconsiderable, being mildest in young children from 1 to 6 years of age. After the beginning of these protective vaccinations, a distinct subsidence of the epidemic was observed, at a season of the year, moreover, when personal exposure was increased, that is, at Christmas and New Year.

Protection against diphtheria needs not only the activity of an efficient health board but also the assistance of the private physician;

48. McClelland, J. E.: Diphtheria Preventive Work in Cleveland Public Schools, Ohio State M. J. **19**:328-331 (May) 1923.

49. Boudreau, F. G.: Modern Methods in the Prevention of Diphtheria, Ohio State M. J. **19**:107-110 (Feb. 1) 1923.

50. Vogel, C. C. C.: Experience with Injection of Diphtheria Toxin and Antitoxin, Ugesk. f. Læger **85**:111-112 (Feb. 15) 1923.

it is from him that advice is sought on these subjects. After showing the prevalence of diphtheria and the results achieved by toxin-antitoxin administration, Neff [51] draws the following conclusions: (1) The medical profession should be aroused to the need and usefulness of active immunization to diphtheria; (2) routine private practice must include the education of families in the use of toxin-antitoxin. It is obvious that the medical profession will be the final authority with the public as to the desirability of diphtheria immunization; (3) the systematic administration of toxin-antitoxin is easy, and if employed in private practice the demand for it will eventually reach throughout the community; (4) the use of refined toxin-antitoxin as now available is safe, and the physician need have no hesitancy in making diphtheria immunization a part of his regular work; (5) it is conservative to state that 90 per cent. of persons receiving toxin-antitoxin develop immunity. There are a few recognized exceptions; (6) no child should be accepted as immune until a negative Schick test is obtained.

Schroder and Park [52] compare the merits of new and old preparations of diphtheria toxin-antitoxin. The toxin-antitoxin mixture first used by the New York City Health Department in its campaign against diphtheria, started in 1914, contained 3 L + doses of toxin per cubic centimeter, with sufficient antitoxin to reduce the toxicity so that 1 c.c. of the mixture caused paralysis in a guinea-pig in about twenty-five days. This mixture gave a satisfactory rate of immunity, but the number of painful reactions made its use unpopular. An attempt was then made to reduce the toxicity of the mixture and yet secure the same degree of protection. After experimenting with various strength doses, a mixture containing 0.1 L + dose of toxin, one-thirtieth of the original amount, was found to give practically the same percentage of immunization and at the same time reduce the number of local reactions almost to nil. The authors conclude that the new mixture containing only 0.1 L + dose of toxin with antitoxin gives the same immunizing results as the older 3 L + mixture. The local inflammatory reactions are few and are practically never seen in children with the new mixture. The latter preparation is now used in routine work by the New York Health Department.

Evidence is brought forward by Glenny [53] and his associates to show that the toxicity test alone may give incomplete or erroneous con-

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51. Neff, F. C.: Active Immunization Against Diphtheria in Private Practice, J. A. M. A. **81**:738-741 (Sept.) 1923.

52. Schroder, M. C., and Park, W. H.: Comparative Merits of New and Old Preparations of Diphtheria Toxin-Antitoxin, J. A. M. A. **81**:1432-1435 (Oct. 27) 1923.

53. Glenny, A. T.; Allen, K., and Hopkins, B. E.: Testing the Antigenic Value of Diphtheria Toxin-Antitoxin Mixtures, Brit. J. Exper. Path. **4**:19-27 (Feb.) 1923.

clusions as to the immunizing value of a toxin-antitoxin mixture, intended for immunization against diphtheria. Four methods are described for testing the antigenic value of mixtures: (*a*) Tracing the antitoxic value of the blood of rabbits after a single subcutaneous injection of the mixture as a "primary stimulus"; (*b*) accelerating the results of (*a*) by a subsequent injection, as a "secondary stimulus," of either the same mixture or of a Schick dose of toxin; (*c*) tracing the increase in antitoxic values of the blood of immune rabbits after a subcutaneous injection of the mixture as a secondary stimulus; (*d*) injecting guinea-pigs, which have survived the test for toxicity of the mixture, with Schick doses of diphtheria toxin at weekly intervals, commencing three weeks after the injection of the mixtures.

Ruh and McClelland [54] have compared diphtheria immunity in the mother and in the new-born. The question of transference of antibodies, protein sensitization and infection from mother to child has been much studied. It is well known that a large percentage of new-born infants are immune to diphtheria. How do they get this antibody, and how does the percentage of immunity compare with the percentage of the mothers' immunity? The antitoxin content of the blood of the mother and the babe has been previously studied and found to be almost identical. But intradermal tests did not give similar results. There are certain technical difficulties with the Schick test in the new-born that make the results uncertain. The skin does not readily form a wheal and the bleb disappears quickly.

Schick tests were made on 100 mothers and new-born babes. All babies were under the age of 7 days, and some had not yet nursed. The reactions of seventy-six mothers and seventy-nine babes were negative; twenty-four mothers and twenty-one babes gave positive reactions. The positive skin tests on the infants were usually not so intense as those of the mothers. There is a close agreement of reactions between mothers and the new-born. Eight of these negative infants had not nursed. It is evident that they must have received their antitoxin before birth through the placental circulation.

Kellogg [55] has devised a new method for determining human susceptibility to diphtheria. The test consists in the injection into the skin of a white guinea-pig, a mixture of equal parts of serum from the patient to be tested and a toxin solution containing $\frac{1}{30}$ unit of antitoxin for each cubic centimeter. If the serum contains $\frac{1}{30}$ unit of antitoxin

54. Ruh, H. O., and McClelland, J. E.: Comparison of Diphtheria Immunity in the Mother and in the New-Born, Am. J. Dis. Child. **25**:59-62 (Jan.) 1923.

55. Kellogg, W. H.: Intracutaneous Guinea-Pig Test (Kellogg) for Human Susceptibility and Immunity to Diphtheria, J. A. M. A. **80**:748-750 (March 17) 1923.

per cubic centimeter, 0.1 c.c. will contain $\frac{1}{300}$ unit of antitoxin; 0.2 c.c. of the mixture will contain $\frac{1}{300}$ unit of antitoxin and $\frac{1}{300}$ L + dose of toxin. The combining ratios of these substances is such that there will be free in the mixture $\frac{1}{300}$ minimal lethal dose of toxin. This is just sufficient to produce redness without necrosis in the skin of the guinea-pig. If necrosis appears, there is less than $\frac{1}{30}$ unit of antitoxin per cubic centimeter of serum, and the subject is not immune. In a series of 160 tests, the Schick and Kellogg tests agree in all but two instances. Kellogg's conclusions are: 1. The test described is conclusive as showing either the presence or the absence of immunity to diphtheria. 2. Controls are possible which guard against deteriorated toxin and false negative reactions. 3. False negative reactions with the technic described are believed to be an impossibility. 4. Protein reactions do not occur. 5. The test is a central laboratory one, relieving the physician of the responsibility for the interpretation of the doubtful reactions so frequently observed in the Schick test. 6. The test is the one of choice for practitioners having occasion to test a few persons at a time. The disadvantage of the Schick test, under such circumstances, is that no control against false negatives from deteriorated toxin exists. 7. The test is not recommended as a substitute for the Schick test, when large groups are being examined, for the reason that the collection of a large number of blood specimens would be too time consuming, excepting with adults and older children with whom venipuncture can be used.

TREATMENT

Roberts,[56] in the New York State Journal of Medicine, has made an analysis of 500 deaths from diphtheria occurring in New York State, excluding New York City, during 1922, with the following conclusions: 1. Diagnosis is not made as promptly as it should be in many cases. Most of the patients are seen later than the second day of the disease, and there is a considerable percentage of late and nearly moribund cases which go to a fatal issue. 2. Any child, seen at any stage having sore throat with what looks like a patch, membrane, high fever and prostration, should receive antitoxin at once, regardless of laboratory diagnosis. Waiting for a report on the culture, and failure to give antitoxin at once, were definite factors in the deaths of at least 80 per cent. of the patients in the 500 reported. 3. If there is time, it is advisable to "desensitize" patients giving a history of asthma, or those who have had antitoxin before. In the 500 deaths analyzed, the intravenous method is said not to have been used on the first day of the

56. Roberts, B. E.: Analysis of 500 Deaths from Diphtheria Occurring in New York State (exclusive of New York City) in 1922, New York State J. M. **23**:452-460 (Nov.) 1923.

disease in a single instance. Antitoxin was usually given intramuscularly.

In the laryngeal patients it is probably better to do either intubation or tracheotomy promptly, for, of 110 deaths from laryngeal obstruction, fifty-eight did not receive this form of treatment. Recently suction has proved helpful in loosening the membrane from the larynx and thus freeing the lower airways. This, of course, is more easily carried out in a hospital with plenty of nurses and doctors in attendance, and, as a matter of fact, it is doubtful whether diphtheria should ever be treated in the home if hospital care can be provided. Too little attention has been paid to patients during convalescence; heart involvement has played a rôle in nearly half of the deaths and, in a goodly number, failure to keep the patient quiet, which means at rest in bed, was definitely mentioned as the immediate cause of a fatal issue.

The Chicago Department of Health has published the following statistics on the value of early antitoxin.[57] Of a total of 8,372 cases of diphtheria, 624 patients were given antitoxin on the first day of the disease with only two deaths. In 2,181 patients, antitoxin was given on the second day with thirty-three deaths, or 1.51 per cent. mortality. In 2,926 patients, antitoxin was given on the third day with ninety-nine deaths, or 3.38 per cent. In 1,578 patients, antitoxin was given on the fourth day with 176 deaths, or 11.15 per cent., and of 1,063 patients, to whom antitoxin was first administered on the fifth day or later there were 234 deaths, or 22.01 per cent. These figures indicate in no uncertain way the importance of early diagnosis and prompt serum administration in diphtheria. It is also believed that the value of the Schick test and the application of toxin-antitoxin is greater even than the therapeutic use of antitoxin.

Forbes [58] tabulates seventeen fatal cases of diphtheria in Brighton, England, showing the time lost by the family physician in each case in giving diphtheria antitoxin. Such delay in many patients results in a fatality which undoubtedly could have been avoided by prompt administration of diphtheria antitoxin.

Ker [59] protests, on grounds of expense, against the Memorandum from the British Ministry of Health in advising an initial dose of 8,000 units of diphtheria antitoxin, when a provisional diagnosis of diphtheria is made. A smaller dose is just as efficient in these doubtful cases and thereby saves government money. If the case is clinically diphtheria, much larger doses, even up to 30,000 and 50,000 unit doses, as the

57. Editorial: Boston M. & S. J. (Sept. 6) 1923.

58. Forbes, D.: Delay in Giving Diphtheria Antitoxin, Lancet **2**:34 (July 14) 1923.

59. Ker, C. B.: Note on Serum Dosage in Diphtheria, Lancet **1**:642-643 (March 31) 1923.

severity of the case seems to warrant, may be given. But in the early doubtful cases, from 2,000 to 4,000 units is just as efficient until a definite diagnosis is made. Then follow with more antitoxin as needed. The main fault with the general practitioner is not in the smallness of the dose of antitoxin administered while waiting for a bacteriologic report, but in not giving any serum at all. If the condition of a patient is suspicious enough for a throat culture, serum should be given at once.

This note from Ker called forth a large number of letters to the editor of the Lancet, both in support and against the Memorandum of the Ministry of Health. These letters put before the medical profession a great deal of valuable information on antitoxin administration from those most qualified to discuss the subject.

Peters [60] protests against Ker's small initial dose recommendation, on the ground of variations in the toxicity of the disease in different years. In his area, the medical officer of health sends notices to the general practitioner of the type of diphtheria prevalent, with suggestions for serum dosage. Such a plan seems wiser than the general advice of 8,000 units initial doses in the Ministry of Health's Memorandum or of Ker's smaller provisional dosage.

Thompson [61] agrees with Ker's idea of saving expense with small initial doses of antitoxin in provisional cases of diphtheria. If Ker, with his experience, sees a patient and says a dose of from 2,000 to 4,000 units is sufficient, we can rely on his judgment. But unfortunately, all of us cannot pick out these mild cases, so that it would seem wiser for most of us to rely on the large initial dose, as advised by the ministry's memorandum. This larger dose of antitoxin would undoubtedly result in a saving of child life, which would outweigh in monetary value the added cost of the diphtheria antitoxin.

Caiger [62] gives further evidence on the desirability of early antitoxin administration: The medical superintendent of a large fever hospital states that of 150 fatal cases of diphtheria during 1922, 30 per cent of the patients died within twenty-four hours of admission, and seventeen more, or 42 per cent., within forty-eight hours. When the efficiency of antitoxin given early is considered, such a report is deplorable. Some of these deaths were due to delay in calling physicians, but far too many were due to a delay on the part of a physician in giving antitoxin when the patient was first seen.

Osgood [63] reports his experience with intravenous antitoxin in fifty-four patients. Time is an important factor in the treatment of diph-

60. Peters, B. A.: Lancet **1:** (April 14) 1923.
61. Thompson, F.: Lancet **1:** (April 7) 1923.
62. Caiger, F. F.: Diphtheria Antitoxin on Suspicion, Brit. M. J. (June 9) 1923.
63. Osgood, H.: Intravenous Use of Diphtheria Antitoxin, J. A. M. A. **81:** 1406-1410 (Oct. 27) 1923.

theria, especially in the late neglected patients. By giving the antitoxin into a vein, the whole amount becomes immediately available for neutralizing the toxin produced by the diphtheria bacilli. Subcutaneous or intramuscular injections of antitoxin are absorbed slowly, as shown by Park's example:

> A child weighing 25 pounds (11.3 kg.), receives 10,000 units of antitoxin. If given subcutaneously in 12 hours there will be 1.5 units per c.c. of blood; if intramuscularly, in 12 hours, 4.5 units and in 48 hours, 4 units; if intravenously, immediately 12 units, and in 48 hours, 8 units.

It is thus seen that the intravenous method makes more antitoxin available for immediate use than the other methods of administration.

A clear serum with a high titer should be chosen. The turbid and low titer serums should be reserved for intramuscular use. Careful asepsis should be observed and the serum given slowly into an arm vein. Frequently it was diluted with physiologic sodium chlorid solution, from eight to fifteen times its volume. In all injections it should be warmed to body temperature. The injection should take from five to fifteen minutes, depending on the amount given. The patient should be watched closely, kept flat in bed and covered warmly. When a chill develops, hot water bottles should be banked along the trunk and extremities, and if the temperature rises, a sponge bath should be given. In a few patients camphor or epinephrin should be given subcutaneously for urticaria or cardiovascular disturbance.

About 50 per cent. of the patients receiving intravenous antitoxin had a chill varying from a slight rigor to a severe chill with hyperpyrexia, tachycardia and cyanosis. A dose of intramuscular antitoxin a few hours preceding the intravenous injection reduced the liability to chill. The physiologic sodium chlorid solution also lowered the percentage of chills. Adults and children reacted in about the same proportion, although the chill in adults might be more sharp than in younger patients. The size of the intravenous dose varied from 800 to 15,000 units, or 24,000 units in two injections. The intravenous combined with the intramuscular injections are the best for general use.

Indications for intravenous injections: 1. Late cases of four to five days' duration, either moderate or severe types with no previous antitoxin. 2. Severe and malignant cases either early or late in the disease. 3. Laryngeal cases secondary to faucial involvement. 4. "Bull neck" cases and those with hemorrhage. 5. Cases that do not respond to ample intramuscular doses.

Contraindications are: 1. Cardiac decompensation or severe organic lesion of heart or blood vessels. 2. Chronic nephritis. 3. Horse serum or protein sensitivity unless the patient can be desensitized.

The careful selection of a proper lot of antitoxin, observance of precautions against allergic shock, and care in the technic of administration

render the intravenous injection of stock concentrated diphtheria antitoxin reasonably safe.

Iversen [64] reviews his experiences with intravenous antitoxin in nineteen cases, and arrives at the same general conclusions as the other investigators. The two objections to the method are, first, the difficulty of administration in young patients and second, the danger following the injections. The first can be overcome by experience usually, and the second by improved technic and further investigations. Unpleasant conditions of collapse may follow the intravenous injections, but these are usually quickly over and camphor subcutaneously is a good remedy in combating this condition. Iversen concludes that intravenous injections of antitoxin are not dangerous and should be the method of choice. Injections should be made slowly and discontinued on the appearance of any reaction.

Benhamou [65] and his associates report several favorable results from intraspinal injections of from 20 to 40 c.c. of antidiphtheritic serum in malignant diphtheria. These treatments were aimed against the intoxication of medullary centers. Intramuscular injections of high doses of serum were used in addition.

Lesné [66] says that as a rule passive immunization by introducing diphtheria antiserum into the intestines is impossible. Certain infants are capable of absorbing the ingested antitoxin, but this is attributed to defects in the intestinal epithelium, insufficiency of gastric juice, or hepatic function, or to more or less latent gastro-intestinal lesions. Older children can be immunized by intrarectal injection of diphtheria antitoxin only when the bowel is diseased. Absolute immunity can be obtained only by subcutaneous, intramuscular or intraperitoneal injections.

Lingeman [67] states that the management of diphtheria in the outlying districts is much more difficult than in the larger cities, where a modern hospital for contagious diseases with a well-trained staff is available. There are few physicians who have had training in intubation outside of these hospitals. This is the most difficult operation in surgery, and requires adequate training for its correct performance. Hospitals for contagious diseases should provide this training for more men, so that there will be more physicians qualified for this operation throughout

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64. Iversen, P.: Intravenous Injection of Serum, Lancet **1**:694-696 (April 7) 1923.

65. Benhamou, E.; Camatte, and Flogny: Paris méd. **13**:382-384 (April 28) 1923.

66. Lesné, E.: Inefficiency of Intestinal Diphtheria Antitoxin Immunization, Bull. et mém. Soc. med. d. hôp. de Paris **47**:679-680 (May 11) 1923.

67. Lingeman, B. N.: Laryngeal Diphtheria in Smaller Communities, J. Indiana M. A. **16**:248-249 (Aug.) 1923.

the country. The family physician should be trained to recognize the disease early. A croupy cough and dyspnea, with both inspiratory and expiratory difficulty, not relieved by ordinary means and which persists in the day time, is always suspicious in a child. Even though the pharynx is clean and cultures are negative, antitoxin should be given. The average family physician does not give sufficient antitoxin to the laryngeal cases. At the Chicago Contagious Hospital, the average dose for the laryngeal patient in 1920 was 29,600 units. Most of the children were aged from 2 to 5 years. When laryngeal diphtheria is suspected, antitoxin should be given immediately. If the family physician is not trained in intubation, he should get in touch with some one who can perform this operation. Everything should be in readiness, such as a sheet with strong safety pins, a little brandy or camphorated oil, and, best of all, a trained nurse, if possible. After intubation, the patient needs especial care and should be within easy access of the surgeon. The tube usually can be removed on the fifth day. If there is a surgeon especially trained for intubation in each community, and if the family physician calls him early, the mortality from this disease should be reduced in the smaller communities.

Purcell [68] finds direct intubation of great value in laryngeal diphtheria. The indirect or O'Dwyer method is apt to cause trauma to the larynx, while with the laryngoscope one can see the conditions present, remove membrane and insert the tube by direct vision. With the bronchoscope one can remove membrane further down and by the two methods many lives can be saved. Purcell advocates the use of antitoxin early and in sufficient dosage. If the condition is recognized and the patient treated in time, the necessity for intubation will be avoided

Gover and Hardman [69] have had considerable success in the treatment of laryngeal diphtheria by suction. The mortality of intubated patients with laryngeal diphtheria in hospital practice varies from 25 to 40 per cent. Removing membrane from the larynx by suction lessens the number of patients needing intubation and thereby lowers the mortality. The method used is by direct laryngoscope, Boyce position, either metal tubes or silk elastic catheters, and a motor-driven suction pump. The tube is introduced under ocular guidance and any mucus or visible membrane removed by suction. It is noted that membrane in the larynx is usually thinner and more loosely attached than that in the fauces. It is frequently loose and flapping, and removal rarely causes bleeding.

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68. Purcell, C. E.: Direct Intubation in Neglected and Desperate Case of Tracheal and Bronchial Diphtheria, South. M. J. **16**:301-304 (April) 1923.

69. Gover, R. W., and Hardman, R. P.: Treatment of Laryngeal Diphtheria by Suction, Arch. Pediat. **40**:170-173 (March) 1923.

The entire procedure requires only a few minutes and the relief is usually immediate and marked. Most of the patients had attacks severe enough to require intubation. Not all are relieved sufficiently to avoid intubation or tracheotomy. Many of them were, and no bronchopneumonia followed the suction method excepting in the tracheobronchial type. In all, fifty patients were treated, with four deaths, a mortality of 8 per cent. Four were intubated before admission, and of these, two died. In the others the tubes were removed and suction used. Of the forty-six remaining, six were not relieved by suction and were subsequently intubated. Of these, one died. The fourth fatality was in a patient of the tracheobronchial type, temporarily relieved by suction.

Treatment by suction may need repetition. In the fifty patients so treated, the average number of times suction was used was less than three. When suction is repeated, it is usually needed about six hours after the first. This may be repeated several times over a forty-eight-hour period. Intravenous antitoxin was given in forty-two cases, the dose varying from 3,000 to 9,000 units. This is believed to be a very important part of the treatment. If the larynx can be kept free from membrane for thirty-six to forty-eight hours, there is not much danger of its re-forming. However, subsequent subglottis edema may be troublesome and require intubation. Suction will not relieve this condition. This treatment should not be attempted except by one experienced in direct laryngoscopy and also one who is able to do a rapid intubation or tracheotomy. A larger experience is necessary before the value of the method can be ascertained, but this preliminary report gives encouraging results.

According to Lay,[70] during the period from 1903 to 1915, the Diphtheritic Department of the Venice Civilian Hospital received 415 patients, including 255 males and 160 females. Of these patients 257 were cured; 158 died from various causes, chiefly bronchopneumonia. During this period (1903-1915), 134 primary tracheotomies were performed, and thirty-one tracheotomies after intubation. Altogether, 240 intubations were done, thirty-one of which were followed by tracheotomy. The tracheotomized patients included 162 deaths, and the intubated ones included fifty-six deaths. Among the intubated patients, ten were intubated a second time; five patients were intubated three times, and four patients, four times. The last nineteen patients all recovered. Deaths among the intubated included thirty-six patients who were intubated once, sixteen who were intubated twice, four who were intubated oftener than twice.

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70. Lay, E. B.: Intubation and Tracheotomy in Treatment of Diphtheria at Venice, Riforma Med. **39**:444-445 (May 7) 1923.

The hospital sojourn of the different patients varied from a minimum of twenty days to a maximum of thirty-eight days. As a sequel of intubation, a transitory pharyngeal paralysis was noted in several instances. Death from heart failure occurred in one instance during convalescence, as a remote complication due to the disease rather than to the treatment. Bronchopneumonia supervened as a complication in 60 per cent. of the tracheotomized patients, aggravating the toxic infectious condition already present, and leading to a fatal outcome.

Von Gröer [71] finds that diphtheria antitoxin acts in the organism of the new-born exactly according to the same laws as have been established for older children (Schick). A "biological peculiarity of the new-born" (Kirstein), departing from this rule, does not exist. The cases observed by Kirstein, of supposedly undoubted diphtheritic infection in naturally protected persons should therefore not be interpreted as meaning that the serum-immune new-born infant has no work to do for its antitoxin. Substances with only an ergotropic—not an antitoxic effect—are unable to substitute the specific antitoxin effect in the organism of the new-born. These substances likewise act in new-born infants just as in the older organism.

637 South Wood Street.

71. Von Gröer, E.: Action of Diphtheria Antitoxin on New-Born, Monatschr. f. Kinderh. **24**:635-640 (Jan.-Feb.) 1923.

News and Comment

CHILD HEALTH MAGAZINE

The January number of the *Child Health Magazine,* published by the American Child Health Association, announces the discontinuance of that Journal with the current number.

This Journal has had only a short existence but has been well edited and will be missed.

RED CROSS BULLETIN

We are in receipt of "The Bulletin of the Save the Children Fund International Union," issued by the International Red Cross.

This bulletin is quite useful for those who are interested in keeping abreast of the various activities for promoting Child Health in countries the world over.

Abstracts from Current Literature

Anatomy and Physiology

THE PRESSURE FACTORS IN THE BILIARY DUCT SYSTEM OF THE DOG. A. WINKELSTEIN and P. W. ASCHNER, Am. J. M. Sc. **168**:812, 1924.

The mechanism affecting the intermittent discharge of bile into the duodenum was studied experimentally on dogs. The quantitative pressure variation existing in different parts of the biliary system and their interrelationship was investigated. Thirteen experiments are cited.

It was found that the pressure in the common duct is low, being from 60 to 65 mm. of bile. It varies little and is only slightly influenced by pilocarpin and respiration. Spontaneous variations in the tonus of the sphincter of Oddi are slight. This tonus is reduced by substances in the gastric chyme and by magnesium sulphate, potassium bicarbonate and bile salts when placed on the ampulla of Vater. The tonus is increased by calcium chlorid used similarly. Pilocarpin increases and atropin and epinephrin decrease the tonus of the sphincter of Oddi when given subcutaneously. This reduction in tonus was never greater than one-fifth.

The musculature of the gallbladder displays tonus variations, but little contractile power. Atropin decreases and pilocarpin increases the tonus of the gallbladder, as it does the tonus of the sphincter of Oddi.

The cystic duct offers little resistance to the outflow of bile from the gallbladder.

A contrary or reciprocal innervation betwen the gallbladder and the sphincter of Oddi could not be demonstrated.

Increased intra-abdominal pressure, chiefly due to the inspiratory phase of respiration, effects a large pressure increase within the gallbladder and almost none in the common duct.

THE PATHWAYS OF THE MEDIASTINUM, THE LUNGS AND THE PLEURA. J. CURTIS LYTER, Am. J. M. Sc. **168**:882, 1924.

The author carried out a series of experiments, to elucidate the apparent migration of tubercle bacilli from the primary lesion in the chest to distant parts of the same side and to the other side. This apparent migration was observed clinically by a series of stereoroentgenograms, taken at regular intervals in those patients revealing a steady progress of pulmonary pathology. The sputums in these cases were continuously negative for tubercle bacilli.

The experiments were carried out on guinea-pigs, rabbits and sheep. In the first series of experiments India ink, or an aqueous solution of charcoal, was injected into the mediastinum at the bifurcation of the trachea. One week after six weekly injections the animals were necropsied. The pigment was found in both lungs and in large amounts beneath the visceral and parietal pleura on each side. None was found beneath the diaphragmatic pleura or in the liver or spleen.

A second series of experiments was carried out similarly, except that the pigment was injected into the right pleural cavity. At necropsy the pigment was again found in both lungs, the quantity in each lung being equal, in the tissues of the mediastinum and beneath the parietal and visceral pleura on each side. As in the previous experiment none was found beneath the diaphragmatic pleura or in the liver or spleen.

The findings were the same in all three animals. In those cases where charcoal was employed, there was the same general gross distribution as with India ink.

Microscopically, the pigment was found chiefly in the intercellular spaces, none in the large lymph vessels or blood vessels and only a relatively small quantity in the macrophages.

From these experiments the author believes that coarse material such as charcoal can migrate from one portion of the thoracic cavity to the other and through the respiratory tissues. He suggests that the mechanism of this migration probably depends more on the physiology of the pulmonary respiration than on phagocytosis or lymph flow, as was formerly conceived.

PARSONS, Ann Arbor, Mich.

THE INFLUENCE OF THE SUPRARENAL GLAND ON THE THYMUS. III. STIMULATION OF THE GROWTH OF THE THYMUS GLAND FOLLOWING DOUBLE SUPRARENALECTOMY IN YOUNG RATS. HENRY L. JAFFE, J. Exper. Med. **40**:753, 1924.

Previous studies in which regeneration of the thymus gland followed double suprarenalectomy in older animals, after thymus involution had normally begun, prompted a similar experimental study on growing animals.

Twenty-five young rats were double suprarenalectomized at ages varying between thirty-five and fifty-four days. The thymus of a normal rat generally reaches its maximum size between the eightieth to ninetieth days of life.

Eleven of the twenty-five rats died from one to forty-one days after operation and were excluded from the experiments proper, the remaining fourteen animals were sacrificed at two week intervals from two to eight weeks after operation. There were fourteen control rats, eleven of which were litter mates of the operated animals.

At necropsy, the thymus gland of each of the fourteen suprarenalectomized rats was heavier than that of its respective control, the difference varying from 12 to 85 per cent. with an average difference of 49 per cent.

The author's conclusions are:

1. Double suprarenalectomy in growing rats is an additional stimulus for thymic growth, and brings about marked prepubertal hyperplasia of this gland.

2. Our results on young rats suggest that the suprarenal cortex may be a factor in the excessive thymic hyperplasias seen in infants and children.

McCLURE, Evanston, Ill.

SITTING HEIGHT OF JAPANESE CHILDREN. YOICHI SEKI, J. Pediat. (Tokyo) **293**: 1309 (Oct.) 1924.

Seki tabulated the measurements of 620 children, who entered the pediatric service of the Kyoto Imperial University Hospital, and also who visited its outpatient department. He found that the average sitting height during the first and second months was 32.6 cm., and the average monthly increase thereafter was 0.075 cm., so that at the end of the first year it reached 44.5 cm. The increase from the second to the fifteenth year was at the annual rate of 2.7 cm. Of the 620 children measured, there were three whose Gelidusi reached 1.00 but the average Gelidusi was 0.94. Seki's Gelidusi approached the formula: Sitting Height^{3} = Weight $\times$ 10.

KATO, Los Angeles.

Pathology, Bacteriology and Biochemistry

PARATHYROID TETANY. DRAGSTEDT, Endocrinology **5**:657-661, 1924.

The author describes a method by which it is possible to preserve from 75 to 90 per cent. of dogs from which both thyroid and parathyroids have been

removed. These dogs were kept free from symptoms of tetany by the following treatment:

A 10 kg. male, or nonpregnant female dog, is placed on a diet consisting of 75 gm. of lactose, 500 c.c. of milk and white bread ad libitum per day. The diet is continued two weeks before operation, the feces becoming liquid, colorless and acid to litmus and the fecal bacteria aciduric in type. After operation, the animal is fed daily with the stomach tube for at least a month. The author states that such a diet checks bacterial proteolysis or putrefaction in the intestinal tract, and accordingly prevents the formation of toxic protein derivatives, the symptoms of parathyroid tetany being thus prevented. Tetany in pregnant dogs cannot be controlled by such dietary methods. The author thinks that the pregnant uterus may supply toxic materials. Parathyroid tetany in pregnant dogs can be controlled by oral administration of calcium lactate and by the intravenous injection of Ringer's solution.

WADDELL, University, Va.

ON THE MECHANISM OF PHLORIDZIN DIABETES. II. THOMAS P. NASH, JR. and STANLEY R. BENEDICT, J. Biol. Chem. **61**:423, 1924.

Ringer has claimed that in phloridzin diabetes there was injury to the pancreas, preventing production of the antidiabetic hormone and that therefore a phloridzinized animal afforded a means of assaying insulin. The authors gave dogs phloridzin, then killed them and extracted the pancreas for insulin. The insulin preparations from these dogs were quite as active as that from normal dogs. The authors do not believe Ringer's view tenable.

THE DETERMINATION OF GASES IN BLOOD AND OTHER SOLUTIONS BY VACUUM EXTRACTION AND MANOMETRIC MEASUREMENT. I. DONALD D. VAN SLYKE and JAMES M. NEILL, J. Biol. Chem. **61**:523, 1924.

These papers deal with a modification of the Van Slyke apparatus. In the previous apparatus, the volume of gas was read off on a buret and corrected to existing barometric pressure and vapor tension. In the modified apparatus, the gas to be measured is brought to a definite volume and then the pressure under which it exists is measured by a manometer. (This abstract also covers the article on page 575.)

HIGGINS, Cincinnati.

STUDIES UPON THE ETIOLOGY OF DENGUE FEVER. I. EXPERIMENTAL TRANSMISSION TO THE LOWER ANIMAL. WILLIAM H. HARRIS and CHARLES W. DUVAL, J. Exper. Med. **40**:817, 1924.

Berkefeld filtered blood serum and whole defibrinated or citrated blood from sixteen patients with typical dengue, which when injected intraperitoneally or intracardially into guinea-pigs was followed in forty-two of 143 animals used in the initial transmission experiment by a reaction closely resembling the symptoms of human dengue, differing only in the absence of exanthem. This reaction consisted of a primary pyrexia, which occurred after an incubation period of from two to five days, with a secondary rise of temperature after a twenty-four to forty-eight hour remission and a concomitant leukopenia. In this experiment reactions were obtained with material from eleven of the sixteen human cases.

Two of the virus strains were propagated through thirty-six and forty-five generations respectively.

STUDIES UPON THE ETIOLOGY OF DENGUE FEVER. II. CULTIVATION AND NATURE OF THE VIRUS. CHARLES W. DUVAL and WILLIAM H. HARRIS, J. Exper. Med. **40**:835, 1924.

The authors describe the cultivation of a minute organism from the blood of dengue patients in Smith-Noguchi mediums, and Noguchi semisolid plasma mixture capped with liquid petrolatum.

These micro-organisms appear as globoid bodies arranged singly, in pairs and in short chains. They pass readily through the Berkefeld filter (N and V), and intraperitoneal injection of the filtrate into guinea-pigs is followed by a reaction identical with that induced by the inoculation of human dengue blood.

While the authors are of the opinion that these micro-organisms may bear etiologic relationship to dengue, they state that they realize that further proof and confirmation of their work are required to establish the connection.

McCLURE, Evanston, Ill.

THE CULTIVATION OF VACCINE VIRUS IN VITRO. FREDERICK PARKER, JR., J. M. Res. **44**:645 (Sept.) 1924.

Vaccine virus was cultivated in tissue cultures of rabbit testis and carried in culture through nine, eight and six generations, the total time of incubation being fifty-four, forty-six and thirty-five days. There was definite evidence that the virus had not merely been kept alive in the cultures, but had definitely multiplied in the tissue cultures.

COOKE, St. Louis.

THE BACTERICIDAL PROPERTY OF MILK. FINN S. HANSSEN, Brit. J. Exper. Path. **5**:271, 1924.

Fresh milk tested during the first four hours showed bactericidal properties against *B. typhosus and B. paratyphosus.* This property was retained after heating to 70 C. for fifteen minutes, thus differing from the bactericidal properties of serum, in which the alexins are much less heat resistant. A temperature of 75 C. for fifteen minutes destroys the bactericidal power of milk. This parallels so closely the heat reactions of the oxidases and peroxidases of milk that the author proposes the possibility of some relation between these enzymes and the bactericidal power.

THE EFFECTS OF LIGHT ON LEUKOCYTES AND BLOOD VESSELS IN THE MESENTERY OF THE LIVING ANIMAL. ARGYLL CAMPBELL and LEONARD HILL, Brit. J. Exper. Path. **5**:317, 1924.

The authors studied the effect of light from quartz enclosed mercury burners and carbon arcs on capillary stasis in the mesenteries of living frogs. This stasis was apparently induced by changes in the leukocytes leading to thrombus formation, although it is probable the endothelial cells were also affected. The rapidity of the appearance of this stasis can be used as a measure of the activity of the light, and under standard light conditions as a measure of accessory influences. The higher the temperature (between 6 to 36 C.) the more rapidly was the stasis produced by the same light. The presence of invisible or red rays in high intensity apparently did not decrease the rapidity of development of stasis. Melanin in suspension screened the passage of ultraviolet rays, while dilute solutions of eosin applied locally to the mesentery sensitized the capillaries so that even visible rays alone produced stasis.

THE REACTION OF THE SKIN TO VACCINIA VIRUS. J. C. G. LEDINGHAM, Brit. J. Exper. Path. **5**:332, 1924.

A careful histologic study was used to check the clinical appearance of lesions produced in laboratory animals by the injection of vaccinia virus. The

lesion produced was an acute infective granuloma, involving primarily the reticulo-endothelial system and not showing any selective affinity for true epiblastic tissue. Precisely similar reticulo-endothelial tissue reactions are produced, no matter whether the reaction occurs at the site of cutaneous, intradermal or subcutaneous inoculation, or at some remote point following intravenous or intraperitoneal inoculation. The author quotes Watanabe as having shown that intravenous injection of vaccinia virus may produce numerous subcutaneous nodules not involving the skin, but the reticulo-endothelial tissue. The localization of these granulomas may be influenced by local irritation, such as shaving and scarification.

HOAG, New York.

BLOOD IN EXPERIMENTAL TUBERCULOUS MENINGITIS. JIRO SHIMA, J. Pediat. (Tokyo) **293**:1366 (Oct.) 1924.

In the blood of adult rabbits suffering from tuberculous meningitis, experimentally produced by injecting live tubercle bacilli into the subarachnoid space, Shima found that the erythrocytes at first remained normal but toward the end the number decreased from 30 to 80 millions per cubic millimeter, while the leukocytes increased for the first two or three days and then decreased for a period of one to three weeks, followed by another increase which remained until death. As to the differential count, the increase in the total leukocytes corresponded with the increase in the pseudo-eosinophils, which in the human blood correspond to the polymorphonuclear cells. The lymphocytes were in reverse proportion to the pseudo-eosinophils. The eosinophils did not show any deviation from the normal, while the mast cells went with pseudo-eosinophils. The monocytes did not show any change. There were occasional basophilic degeneration of red cells and polychromatophilia was noted from time to time.

KATO, Los Angeles.

Nutrition

THE INFLUENCE OF DIET ON LACTATION. FRED L. ADAIR, Am. J. Obst. & Gynec. **9**:1, 1925.

The author in this article attempts to evaluate the effect of dietary changes on human lactation. The observations are based on a series of 400 cases, to which has been added work on a previous group of 300 cases.

In as large a series of patients as this, he feels that the more important factors such as age and parity of the mother, physical characteristics and condition of the milk glands, maternal psychic disturbances, and size and demands of the offspring would be largely equalized and become constant.

In the first series of 300, the diet was the ordinary hospital food which was not recorded or calculated. The 400 cases used for the calculated diets were divided into four groups: a high protein, high carbohydrate, high fat and a balanced diet were used. The babies were weighed before and after nursing and if expression was practiced, this amount was added to the amount ingested at each nursing.

No detailed metabolic work was done on the mothers and no milk analyses were made. The results were interpreted entirely by the effect on the babies, which is really the crucial test of the value of breast milk from either a quantitative or a qualitative point of view.

Both the high fat and high carbohydrate diets, especially the latter, seemed to appeal to the patients more than either the balanced or high protein diets.

The ratio of the caloric intake could be expressed as follows: high protein, 23; balanced, 30; high carbohydrate, 32; high fat, 39. The amount of protein taken, as 42, 31, 31, 33, average fat, 85, 104, 207, 132; and the carbohydrate ratio as 107, 141, 189, 152.

The minimum average weight of the infants occurred on the fourth day in all groups. The average birth weight for the different series was very nearly the same. The initial weight loss was not very different for the different groups, being the least on the high carbohydrates and greatest for the new-born infants whose mothers had a high fat diet. The weight losses were as follows: high carbohydrate, 213 gm.; balanced, 225 gm.; high protein, 238 gm.; hospital diet, 255 gm.; high protein, 264 gm.

In none of the series did the infants regain average birth weight within twelve days. The number of grams short of birth weight were: high fat, 24 gm.; high protein, 32 gm.; hospital diet (10 days) 75 gm.; balanced, 85 gm.; high carbohydrate, 157 gm.

The assumption was made that the calories necessary for a lactating woman at rest would approximate the needs of an individual at work, namely, 2,400 calories. The excess diet (calories) had no apparent effect in stimulating milk production. In fact, a high caloric feeding might even be objectionable in view of the fact of the not infrequent observation that rapid increase in a nursing mother is often associated with a decreased milk supply.

He concludes, therefore, that the high protein, hospital, and balanced diets without increasing caloric intake, meet the needs of both mother and infant, better than either the high fat or carbohydrate diets.

ALLEN, Chicago.

THE TREATMENT OF ANOREXIA NERVOSA IN CHILDREN. BERNARD MYERS, Practitioner **113**:351, 1924.

Since the war, apparently, the number of neurotic children has increased. A rough estimate in a children's clinic, over a period of two years, places their number at 10 per cent. This increase in London has been ascribed to the fear of air raids during the war and to the nervousness of mothers who were pregnant during that period, together with the influence of the shortage of food. These children are unduly excitable with extremely changeable moods. They are apt to be selfish, egocentric, jealous, although usually clever and intelligent. They fatigue easily. They are usually disobedient and show marked negativism. Dreaming and night terrors are frequent, as are nocturnal enuresis and teeth grinding. Convulsions are occasionally observed, and later habit spasm and hysterical manifestations. These children are extremely difficult to feed; they are faddy and particular about their food, and their likes and dislikes are many. A special type (but one frequently seen in this country, incidentally) is the one characterized by the child who so enjoys the effect of his refusal of food upon his parents and other members of the household, that he continues to have an apparent complete lack of appetite, which proceeds from bad to worse, depending on the reaction he is able to elicit from his parents.

The author cites three cases, one in a child as young as 1 year and 5 months. In his treatment he feels the most important factor to be that the mother should realize that she must become firmly but wisely the master. These children quickly read any evidence of indecision in the faces of their parents. This treatment should be begun early if we are to prevent them from becoming adult neurotics or hysterics.

GELSTON, San Francisco.

PROTEIN MILK AS AN INFANT FOOD. S. V. HAAS, L. H. BARENBERG and M. W. BLOOMBERG, Arch. Pediat. **41**:751, 1924.

The authors find that albumin milk, prepared according to the method described, has proved satisfactory for infants up to 2 years of age, and is particularly indicated in gastro-intestinal disorders, marasmus and premature babies, celiac and infectious diseases. It is palatable, well taken after the

first day or two and may be given undiluted even to premature infants. The average gain in weight for all ages was 4 ounces (115 gm.) per week, the minimum 2¼ ounces (64 gm.), the maximum 6½ ounces (185 gm.) per week. It seems to exert a protective action against ketosis, intoxication and gastro-enteritis. The buttocks never become excoriated on this food. Tolerance for this preparation is equaled only by that for breast milk.

CONCENTRATED FEEDING FOR INFANTS AND CHILDREN. T. L. BIRNBERG, Arch. Pediat. **41**:817, 1924.

A description of the preparation of various concentrated foods, with milk as a base, that are in use in feeding infants, is given. The indications for concentrated feeding are: 1. Vomiting. 2. Anorexia and other difficulties of food intake. 3. Dystrophy with little loss of tolerance. 4. Complementary feeding in nursing infants. 5. Exudative diathesis. 6. Enuresis and allied conditions. 7. In exudates without kidney involvement. 8. Asthenic and undernourished children. Concentrated feeding may be of benefit in nervous vomiting, infectious vomiting and in pylorospasm. The before-mentioned conditions react to concentrated feeding more quickly and more successfully than in any other method of infant feeding and should be used more in this country. The supposed dangers of concentrated feeding are largely theoretic. Fourteen illustrative case reports are given.

VON MEYSENBUG, New Orleans.

THE FAT DETERMINATION OF THE DAILY INTAKE OF BREAST MILK. A. HOFMANN, Jahrb. f. Kinderh. **106**:310, 1924.

On account of the fact that mechanical emptying of the breast is not complete, the author devised a method of estimating the fat content of milk taken by the infant in nursing. Samples of breast milk were removed from the breast at several intervals during the nursing period, and the infant weighed before and after each sample, in this way determining the amount of milk taken during each of these periods. The fat content of the milk taken during each period was then calculated from the amount of cream on the nearest sample. This was repeated for each nursing period during the day, and the cream content of the whole twenty-four hour milk supply was calculated. The increase in cream percentage from the beginning to the end of a nursing period is not a straight line, so that methods which estimate the cream content on such a supposition give erroneous conclusions.

The amount of milk taken by the infant at the first morning feeding was not always the largest. The author concludes from this that the nutritional demand may be less at the first feeding of the day than at the second. Detailed tables are included.

SUTHERLAND, Chicago.

Diseases of the New-Born

COEXISTENCE OF CONGENITAL AMPUTATIONS AND SYNDACTYLISM. H. A. COLEMAN, J. A. M. A. **83**:1166 (Oct. 11) 1924.

Congenital amputation of the two terminal phalanges of each finger was present. The thumbs were not involved. Complete syndactylism of the ring and little fingers of the right hand was associated.

A ROENTGENOGRAPHIC STUDY OF THE INFANT CHEST AS SEEN AT BIRTH. W. W. WASSON, J. A. M. A. **83**:1240 (Oct. 18) 1924.

A roentgen-ray study was made of the early lung changes after the first respiratory acts, and during the first two weeks of life. The infants were

roentgenographed immediately after birth, and records were kept of the time interval, of the respiratory activity of the child and whether or not the cord was severed. Successive roentgenograms were made thereafter in five minutes, ten minutes, fifteen minutes, twenty-four hours and before leaving the hospital. A few stillborn infants were also roentgenographed. In the stillborn child, the chest was uniformly dense, the heart and pulmonary structures being obliterated. Following attempts at resuscitation, the roentgenograms showed air, not only in a portion of the lungs but also in the abdomen. With the onset of respiration, the lung structure began to appear and in some cases the lungs gave the appearance of full expansion within five minutes after delivery. In other cases, more particularly in the prolonged and difficult labors, expansion took place slowly, leaving entire lobes atelectatic or only scattered areas of atelectasis. The density of the areas was comparable to the density of the stillborn lung. The bases were the last to expand, with the lateral borders probably being first. The interval of time for complete expansion to take place varied from five minutes to two weeks. There was a corresponding change in shape of the chest, due to the change in angle of the ribs. Simultaneously with the appearance of air in the lungs, air appears in the stomach. At two weeks the hila have a fairly uniform density without evidence of irregular densities which might be considered as glandular tissue. The linear markings with their columns of air may be well traced to the periphery and are quite prominent. The periphery of the lungs is uniformly clear with an occasional septal marking. The prominence and extension of the hilum shadows to the periphery is attributed to the improvements in the detail of making the exposures.

BONAR, Salt Lake City.

AIR EMBOLISM IN NEW-BORN AND INFANTS AND ITS MEDICOLEGAL ASPECTS. A. LINDBLOM, Virchows Arch. f. path. Anat. **252**:197, 1924.

The author collected six cases from the literature and added a case of his own. In five of these cases, the emboli are apparently explained on the basis of increased intrapulmonary pressure. In four of the cases, this was associated with interstitial emphysema. That air may enter the blood stream through an injured cord is regarded as possible but more difficult to prove. Strangulation, attempts at resuscitation, such as swinging (Schultze's method), forced air insufflation are likely causes of increased intrapulmonary pressure. In making the diagnosis, two possible sources of error must be eliminated, that of introducing the air at the time of the protocol, and the possible occurrence of gas caused by a decomposing body.

SCHWARTZ, Milwaukee.

Acute Infections

A STUDY OF RHEUMATIC NODULES. JAMES H. WALLACE, Arch. Pediat. **41**:731, 1924.

In a series of 124 cases of rheumatism, an analysis showed that there were fifteen patients with rheumatic nodules, nine occurring in children aged from 9 to 12 years. There were eight cases in girls and seven in boys. Only one of the fifteen children gave no history of rheumatism; none gave a history of chorea. All of the fifteen patients showed signs of endocarditis, the heart changes indicating serious cardiac damage in most of them. In ten there was positive evidence of pericarditis, in three more it was probable, in two no evidence of it was found. The number of nodules present at one given time in individual cases varied from one to fifty. The site of predilection is on the elbow, thirteen of the fifteen patients having nodules in this location. The evidence presented shows that nodules occur not infrequently in Chicago, that they are usually associated with endocarditis and frequently with pericarditis and that prognostically they may be considered a grave omen.

A Study of Pneumonia in Infants and Children. R. D. Moffett, Arch. Pediat. **41**:743, 1924.

Reviewing 437 patients with pneumonia admitted to the pediatric service of the Lenox Hill Hospital from 1915 to 1923, it was found that 218 cases were of the lobar type and 199 were bronchopneumonia, which is contrary to the usual teaching in regard to the pneumonias of children. The mortality in the bronchopneumonia cases was 7.1 per cent. and in lobar pneumonia it was 12.9 per cent. The influenzal pneumonias were severe, but the mortality was low. Blood counts showed uniformly high white counts in lobarpneumonia and relatively low counts in bronchopneumonia. In 247 patients the roentgen-ray markings were clear. Beginning the treatment with a definite program of stimulation, accompanied by careful nursing, carried the patient through the disease in better condition and lessened the mortality.

Von Meysenbug, New Orleans.

Observations on the Diphtheria Carrier as an Agent in the Spread of Diphtheria. F. M. Meader, J. A. M. A. **83**:1132 (Oct. 11) 1924.

From the observations made by the Detroit Department of Health, it would appear that diphtheria patients are more likely to be instrumental in the spread of the disease than are diphtheria carriers. Meader is of the opinion that carriers of diphtheroids who have not come in contact with clinical cases of diphtheria may be disregarded from a public health standpoint.

Bonar, Salt Lake City.

Lesions of the Aorta Associated with Acute Rheumatic Fever, and with Chronic Cardiac Disease of Rheumatic Origin. Alvin W. Pappenheimer and William C. Von Glahn, J. M. Res. **44**:645 (Sept.) 1924.

A comparative histologic study of the aorta was made in a series of seventy-seven nonrheumatic patients dying from a variety of causes. An equally large series of syphilitic aortitis patients was studied for comparison. Certain lesions were found in a much higher percentage in the rheumatic patients than in the controls, and so far as their observations go, appear to be characteristic of rheumatic infection. The most distinctive lesions were (1) dense scars in the vicinity of the nutrient vessels, often acellular, and (2) Aschoff cells or nodules in the adventitia.

Cooke, St. Louis.

Measles, Scarlet Fever, Diphtheria and Whooping Cough from 1870 to 1919 in the City of Basel. Ernst Jessen, Schweiz. med. Wchnschr. **54**:1165, 1924.

Measles.—In fifty years, 34,464 cases of measles were reported, 79.7 per thousand inhabitants. There were 931 deaths, or 2.5 per cent. Thirteen thousand six hundred and seventy-nine occurred between the ages of 2 and 5; 13,679 between the ages of 5 and 10. In the first year of life, there was a 32 per cent. mortality; in the second year 20.2 per cent., between 2 and 5 years, 2.6 per cent., and between 5 and 10, only 0.3 per cent. In the first two years, the disease appeared slightly more lethal in the female sex.

Scarlet Fever.—Between the years 1875 and 1919, were reported 11,894 cases of scarlet fever, 27.3 per thousand inhabitants, of which 3,428 occurred during the first 5 years; 6,843 between 6 and 15 years; and 1,523 in persons over 15 years. These figures corroborate the established fact that scarlet fever is preeminently a disease of the school child. The average mortality was 3.7 per cent. The greatest mortality occurred in children under 5 years. The disease was more disastrous to the male sex.

Diphtheria.—In forty-five years 14,521 cases of diphtheria were reported, 33.6 per thousand inhabitants. The average mortality was 7.4. A striking decline in the death rate was noted following Von Bering's discovery. The greatest mortality occurred in the second year of life, next between the ages of 2 and 5. Nurslings were noted to be comparatively immune. The disease appeared to be more lethal to the male sex at all ages, although the female sex was found to be more susceptible.

Whooping Cough.—The average incidence of whooping cough for forty-five years was 36.9 per thousand inhabitants. The average mortality was 4.9 per cent. The most susceptible age was found to be between 2 and 5 years. The greatest number of deaths occurred in the first year of life. The female sex was found to be more susceptible and suffered the greater number of deaths.

It is heartening to note that with the progress of years the introduction of newer therapeutic measures and modern hygiene has perceptibly reduced both the incidence and mortality of all four diseases.

Comparisons.—In forty-five years for all Switzerland, the following mortality figures are given: diphtheria, 43,801; whooping cough, 26,102; measles, 17,315, and scarlet fever, 11,653. Comparative figures are given for the following localities; Stockholm, Chicago, Hamburg, Bremen, Prussia, England and London.

ELTERICH, JR., Pittsburgh.

Chronic Infections

THE KAHN PRECIPITATION TEST AS A ROUTINE TEST IN THE DIAGNOSIS AND TREATMENT OF SYPHILIS. WILLIAM LEVIN, Northwest Med. **23**:543 (Dec.) 1924.

Levin correlates the results of 2,542 simultaneous Kahn and Wassermann tests. He found complete agreement in 92.2 per cent. of his cases, doubtful agreement in 2.3 per cent., and complete variance in 5.5 per cent. The disagreement occurred for the most part in treated syphilitic patients. Two cases of untreated congenital syphilis in infants gave positive Kahn reactions where the Wassermann was negative. A table of comparative results of fifteen other authors is given, showing agreement in from 60 to 98.7 per cent. of cases. A list of references is given.

SCOTT, Philadelphia.

TUBERCULOSIS AS THE CAUSE OF MALNUTRITION IN THE CHILD. A. H. SHENNAN, Practitioner **113**:434 (Dec.) 1924.

This article is an appeal for a more thorough examination of children with so-called "malnutrition." The author feels the most important causes of this defect are tuberculosis, underfeeding, anomalies of heart and alimentary tract and syphilis. There is difficulty in making a diagnosis of tuberculosis in children aged from 3 to 8 years because of the variability of signs. There are five points of importance to be considered of aid in such a diagnosis, namely: (1) a positive skin tuberculin reaction, (2) a definite history of exposure (3) constitutional signs and symptoms, especially lassitude and failure to gain weight, (4) presence of enlarged bronchial glands, (5) lack of other evidences of toxemia.

The author feels that: "If there are no constitutional symptoms, active tuberculosis is not present." These general disturbances are loss of weight or failure to gain, rise in temperature, lassitude and night sweats. Physical signs are exceedingly variable and, as every one knows, the general appearance may be caused by a number of physical abnormalities unassociated with tuberculosis.

The author's treatment consists of institutional care for the patients with definitely established symptoms, and for the uncertain ones, great attention to diet, fresh air, the administration of cod liver oil and repeated examination.

GELSTON, San Francisco.

RADIOLOGIC STUDY OF THE AORTA IN THE INFANT AND ITS DIAGNOSTIC IMPORTANCE IN HEREDITARY SYPHILIS. E. A. BERETERVIDE and J. J. BERETERVIDE, Rev. Soc. méd. arg. **37**:55 (Aug.) 1924.

In the course of a study of measurements of the heart cavities in infants, both under normal conditions and in the various valvular conditions, the authors made some interesting observations on the aorta.

They found abnormal shadows in the aortas of some of the infants, and along with these, considerable increase in the dimensions of the vessel. They were able to establish the fact that a definite relationship existed between syphilitic infection and an increase in volume of the infant's aorta and the definite development of the peculiar shadows observed.

The authors collectively designate these findings as the "radiologic sign of the aorta." They have never failed to observe this sign if the diagnosis of syphilis was definitely established, and regard its presence as conclusive proof of the existence of this condition in the infant.

The findings to date are based on 462 observations. Careful clinical examination of the hereditary syphilitic infant will commonly show some auscultatory modification of the heart sounds, particularly over the left side of the heart in the area corresponding to the pulmonic sounds of the adult. This modification consists in reduplication and at times considerable accentuation of the second sound over this region. The first sound becomes faint and often changes to a soft systolic murmur.

It is in the infant with these clinical findings, soft systolic first sound with absence of any clinical sign or other evidence pointing to lesions in the pulmonary artery, that the authors have found their characteristic radiologic findings, namely, considerable enlargement of the aorta and remarkably abnormal shadows. The authors conclude that the lesions which account for these clinical findings are in the aorta and not in the pulmonary vessels, and occur only in the infant definitely affected with syphilis, and are manifestations of an aortitis similar in all respects to the condition found in the adult.

They regard the radiologic sign as a diagnostic sign of the greatest importance in the diagnosis of hereditary syphilis and one that will be present most constantly.

Under consistent intensive and energetic treatment, the progress of the disease is readily arrested and the prognosis for complete recovery is good.

SCHLUTZ, Minneapolis.

ON THE SEDIMENTATION OF ERYTHROCYTES IN THE BLOOD OF CHILDREN HAVING CONGENITAL SYPHILIS. G. GELBJERG-HANSEN, Ugesk. f. Læger **51**:1011, 1924.

It is a known fact that the sedimentation of erythrocytes in the blood of children suffering from congenital syphilis is very rapid, namely, from ten to twenty-five minutes as compared to five to ten hours in normal children during the first two months of life.

The author has studied nine infants from the fourteenth day to the fifth month, and comes to the conclusion that his blood findings run parallel to the Wassermann reaction. In some instances it was noticed that the rapid sedimentation of erythrocytes occurred before any signs of congenital syphilis became apparent or before the Wassermann reaction was positive; also that the blood condition gradually approached the normal when treatment was instituted.

In some instances, where other tests cannot be undertaken, this may prove to be a splendid diagnostic aid. The instruments needed are easily procured and the technic of the test is simple.

THE EXPERIMENTAL BASIS FOR THE SANOCRYSIN TREATMENT OF TUBERCULOSIS. HOLGER MOLLGAARD, Ugesk. f. Læger **52**:1035, 1924.

The physical and chemical properties of "Sanocrysin," a sodium auric thiosulphate salt, are described. The most interesting of these properties are: (1) Diffusibility of the complex containing the metal ion; (2) inhibition of growth, destruction of the acid fastness and finally fragmentation of the tubercle bacilli; (3) production of an increase in permeability of the lipoid system; (4) solubility in water and a nonprecipitating effect on proteins.

Intravenous injections of this salt were first tried out on healthy calves, and its influence and action were carefully observed on the erythrocytes and hemoglobin, blood pressure, temperature, kidney, liver, growth, weight and gastro-intestinal tract. It was found that the kidney was sensitive to the salt when the dose was more than 0.01 gm. per kilogram of body weight. However, tolerance for higher concentrations of the salt could be obtained by a gradual increase in dosage, except where arsenic had also been given.

Valves with induced tuberculosis showed a very marked reaction to the injected salt. This reaction the author considers to be due to the liberation of the endotoxin from the tubercle bacilli, and not to any toxic effects that the gold salt may have upon the tuberculous animal. The serious complications arising from the liberated endotoxin were prevented by the giving of an antitoxin serum. The amount of serum necessary depended entirely on the endotoxin liberated, the index of which was a gradual fall of blood pressure and increasing albuminuria.

The author, finally, wishes to convey the idea that a rational therapy of tuberculosis is yet to be sought, and that many problems of importance must be solved before the exact value and limits of the serum and gold salt treatment can be ascertained.

SCHLUTZ, Minneapolis.

Internal Diseases

VOLUME AND COMPOSITION OF BLOOD IN ADDISON'S DISEASE. GEORGE E. BROWN and GRACE M. ROTH, Am. J. M. Sc. **169**:47, 1925.

The authors review the literature on the composition of the blood in Addison's disease. On account of the diversity of opinion as to blood volume and the presence of anemia, they undertook the study of the blood in this condition.

Results of seventeen cases are reported, all typical except one.

Definite anemia was found in only one patient.

A mild or questionable anemia was found in four.

In three of five patients, the cell volume index was decreased and in three the saturation index was increased, indicating small erythrocytes with high hemoglobin content. A relatively high lymphocytosis was present in the majority of cases. The blood and plasma volumes were found to be normal in all but one patient, using the dye method.

Decreased percentages of water and blood were observed in one, during the period of acute suprarenal insufficiency.

The authors conclude that anemia, when it occurs in Addison's disease, is apparently not due to dilution or an increase in total blood volume, since large blood volumes did not exist in the presence of anemia. Anemia was not marked by contraction of blood volume, since normal blood volumes existed in all patients in which hemoglobin values were normal.

PITFALLS IN THE DIAGNOSIS OF DIABETES. HENRY J. JOHN, Am. J. M. Sc. **169**: 102, 1925.

The author stresses the importance of correlating blood sugar and urinary findings in the diagnosis of diabetes mellitus. The renal threshold varies widely in normal as well as in diabetic persons. In ninety patients with normal or decreased blood sugar, glycosuria occurred. In fifty-nine diabetic patients with increased blood sugar the urine was normal. Glycosuria may also be alimentary. A diagnostic conclusion cannot be based on a single urine or blood sugar estimation.

A fasting blood sugar and urine examination is not sufficient for diagnosis, unless the blood sugar is high. In this case the patient is certainly diabetic, whether there is glycosuria or not. If the blood sugar is normal or low, no conclusion can be reached regardless of the absence or presence of glycosuria. Diabetic patients on a regulated diet may have a normal blood sugar. The author believes that a blood sugar specimen taken three hours after a heavy carbohydrate meal yields the most valuable information from a diagnostic standpoint. An elevation of blood sugar at this time indicates diabetes.

The author believes that the microchemical methods of blood sugar estimation are inaccurate. The macrochemical methods are preferable.

PARSONS, Ann Arbor, Mich.

A CLINICAL REVIEW OF INTUSSUSCEPTION WITH REPORT OF CASES. EUGENE H. SMITH, Arch. Pediat. **41**:763, 1924.

A striking uniformity of symptoms renders the diagnosis of most cases of intussusception comparatively easy. The symptoms of sudden onset, pain, vomiting, shock, tumor and bloody stools were present in all of the ten cases reported. The degree of shock varies greatly and is not always proportional to the extent of the intussusception. Blood passed by rectum in the early stages is brighter and contains less mucus and more watery fluid, than is commonly seen in the dysenteries.

IDIOPATHIC STREPTOCOCCIC PERITONITIS IN INFANTS, WITH REPORT OF A CASE. J. L. LANDE and R. H. MCBRIDE, Arch. Pediat. **41**:785, 1924.

A girl, aged 5 months, was admitted to the hospital because of malnutrition, failure to grow and abdominal distention. The physical examination showed great loss of weight, marked pallor and abdominal distention. The white count was 14,000 with 65 per cent. neutrophils. At necropsy the intestines were found stuck together by a partially organized fibrinous exudate and a large quantity of greenish pus was found in the region of the spleen. Cultures from this showed streptococcus. The absence of any focus of infection apparently establishes this as a case of idiopathic peritonitis.

ENDOCRINOLOGY IN PEDIATRICS, WITH SPECIAL REFERENCE TO THE HYPOPLASTIC-DYSPITUITARY TYPE OF CHILD. H. L. DOWD, Arch. Pediat. **41**:801, 1924.

Persons of all ages may be abnormal or inadequate because of glandular deficiencies. Children of the status thymicolymphaticus type, frequently overweight, sometimes tall, slender and loosejointed, are a difficult problem of adjustment. The nature of their growth and development renders them frequently self-conscious, inadequate, prone to injury and with a low resistance to infection. They can be assisted more rapidly to a condition of normality by a study of their internal secretions, with the administration of appropriate glandular extracts, than by relying entirely on measures relating to diet

and hygiene and correction of physical defects. Even the cretins are not the simple cases of thyroid deficiency that they have always been considered. They are hypoplastic and their trouble is a pluringlandular one. Such conditions as epilepsy have some relation to disturbances of the internal secretions that warrant further study. Pituitary extracts have a distinctly favorable influence on fatigue and on such symptoms as headache and bed-wetting when used in proper amounts, and can aggravate the condition if an overdose is given. It is a temptation for a gland enthusiast to believe that altered internal secretions are responsible for all human ailments, but a mean between extremes is possible and many children can be made happier and more efficient by the proper use of glandular extracts. Standard potent products must be used if success and uniform results are to be obtained.

VON MEYSENBUG, New Orleans.

FOREIGN BODIES IN RESPIRATORY AND UPPER DIGESTIVE TRACT. SIMON JESBERG, California & West. Med. **23**:52, 1925.

Jesberg reports forty cases, and calls particular attention to the following important essentials. In bronchoscopic work, a specialist should be called; the amateur is surrounded by too many pitfalls and dangers to ensure even a fair measure of success. Teamwork is essential. Haste should be avoided; time should be taken to make a routine study of the case. Delay is never as dangerous as haste; if the larynx is obstructed and suffocation impending, perform a tracheotomy and then take time to study the situation. Distally lighted instruments have many advantages over those illuminated from reflected light in the handle, as the light is always on the field of operation, and is not intercepted to any great extent by the inserted forceps. Physicians are usually slow to consider the possibility of a foreign body unless there is history of its entrance, notwithstanding suggestive symptoms. Suspicion should be aroused in atypical instances of lung infection and roentgen-ray examination made. In the trachea, a foreign body causes coughing, particularly when moved by respiratory air blasts. The movement can be heard with a stethoscope over the sternum. The foreign body does not remain long in the trachea. If its size permits it enters a bronchus and travels as far down the tracheobronchial tree as possible. Inflammatory changes vary greatly, according to the nature of the body and degree of obstruction. Certain vegetable substances set up a violent reaction in a few hours. All cause suppuration eventually. As suppuration results below an obstructed bronchus, clinical signs of pneumonia, with fever, rapid pulse, rapid respiration and cough are manifested. The breath has a fetid odor and there is profuse expectoration of foul pus. If drainage is not established by removal, tissue destruction results, forming a lung abscess. Bodies in the esophagus, if smooth, and not causing complete obstruction, may be tolerated for a long period of time with but slight symptoms. No patient should be operated on without a roentgen-ray examination.

Of the forty cases cited, thirty were children ranging in age from 6 months to 15 years of age.

The foreign bodies recovered included open safety pins, pins, tacks, nails, coins, metal disk from electric switch box, large ball bearing, metal curl from lathing tool, seeds, beans, peanuts and buttons. A diagnosis of foreign body was not made in some of the patients ranging in age from 2 weeks to 9 months.

No anesthetic was given in sixteen patients. Ether was given in five, chloroform in one, local anesthetic, butyn, 5 per cent. in eight. There were two deaths in thirty of the patients.

AN UNUSUAL CASE OF PYLORIC STENOSIS. ALANSON WEEKS and LEROY BROOKS, California & West. Med. **23**:65, 1925.

The patient was a boy, born two months prematurely, weighing 3¾ pounds (1.7 kg.). The child retained food well and had normal bowel movements. On the thirtieth day he began to vomit and thereafter regurgitated part or all of every feeding. Vomiting became at times projectile, stools less frequent and finally there were none for several days. The child was very much dehydrated and weighed 4 pounds (1.8 kg.) when admitted to the Children's Hospital, San Francisco, on the thirty-fifth day. Thick feedings and fluids were tried, both subcutaneously and intraperitoneally. Some improvement was noted for a few days when the vomiting returned. The temperature was 101 and 102, but the infant was somewhat better because of fluids given. On the forty-fourth day, the Fredet operation was performed, and 4 ounces of 3 per cent. glucose solution beneath the skin in the axilla and groin was given before the child left the operating room. A rectal drip of 3 per cent. glucose and 3 per cent. soda solution was also given, and feedings were started three hours after the operation on 3 per cent. glucose, gradually working back to the standard formula.

The temperature rose to 106 F. three days after the operation. The daily rise in temperature gradually subsided, and the patient was discharged in twenty days, weighing 5 pounds (2.3 kg.) and in excellent condition.

JEIDELL, Salt Lake City.

MEDICAL ASPECTS OF ACUTE APPENDICITIS IN CHILDREN. JOHN HOWLAND, J. A. M. A. **83**:961 (Sept. 17) 1924.

Howland calls attention to the frequency with which the intestinal parasites, particularly oxyuris, are found in acute appendicitis, and considers this high incidence strong evidence of an etiologic relationship. One of the chief requisites for the diagnosis of appendicitis is appreciation of the fact that it may be a possibility. Abdominal pain with constant crying and sleeplessness and screaming on defecation or urination are suggestive symptoms. Rigidity is difficult to elicit. Rectal examination is indispensable. Appendicitis is most often confused with pneumonia. With appendicitis, the child is usually pale rather than flushed; is quiet rather than restless and irritable, and breathing is of the costal rather than diaphragmatic type. At best, however, the diagnosis is difficult and affords the physician a complicated problem. With early diagnosis and operation, the mortality should be less than with the adult.

ACUTE APPENDICITIS IN CHILDREN. RICHARD W. BOLLING, J. A. M. A. **83**:963 (Sept. 27) 1924.

The author states that after the first year of life, acute appendicitis is the most frequent abdominal disease of an urgent nature. His personal experience with 123 cases is detailed. Eighty-one of the children were aged from 6 to 15 years. In 60 per cent., abscess or contamination of the peritoneum necessitated drainage. The complications were of the usual variety found in adults, with the exception that postoperative ileus was infrequent. The mortality was 2.5 per cent. in those from 6 to 15 years, while in those under 6 years it was eight times as great. In this group, over 90 per cent. were admitted with a ruptured appendix and peritonitis. The late recognition of the disease is the cause of the high mortality rather than the rapidity of the course or the lack of bodily resistance. The author stresses the danger in administering cathartics in cases of abdominal distress, and states that there is no exception to the rule that acute appendicitis demands immediate surgical attention at any stage.

CHRONIC APPENDICITIS IN CHILDREN. CHARLES G. MIXTER, J. A. M. A. **83**:967 (Sept. 27) 1924.

While the author is not as skeptical as many with regard to chronic appendicitis, he is of the opinion that the condition should be diagnosed only after every other possibility has been excluded. He has made a study of the records of 100 cases of chronic appendicitis in children under 13 years of age. The vast majority were over 5 years of age. In 92 per cent., abdominal pain was complained of, but in only half of this number was the pain referred to the right lower quadrant. Tenderness over McBurney's point was demonstrated in 59 per cent., while in 25 per cent. the abdominal examination was entirely negative. Vomiting, constipation, and headache were also present in many. Follow-up reports of fifty cases revealed the fact that in 62 per cent., the parents considered the operation completely successful, observed improvement in 28 per cent. and failure in 10 per cent.

BONAR, Salt Lake City.

OSTEOGENESIS IMPERFECTA. H. H. SKINNER, Northwest Med. **23**:552 (Dec.) 1924.

Skinner reviews the history, etiology, micropathology, symptoms and treatment of osteogenesis imperfecta. He reports a case in a new-born infant, occurring during or before birth. The child was born with five fractures and died at the age of one year: during this time the child showed thirty-five fractures. The fractures were usually preceded several days by a definite intestinal derangement. There was rapid and ample callus formation. The skull bones were membranous and the sclerae were blue.

SCOTT, Philadelphia.

HENOCH'S PURPURA. JOHN GRACIE, Practitioner **113**:419, 1924.

The author reports two cases of Henoch's purpura. The first patient was a girl, aged 12 years, with a history of recurrent pains, swelling in the knees followed shortly after by spots on the extremities and buttocks. There was no temperature and the girl was not anemic on examination. The petechial hemorrhages were noticed in the before-mentioned distribution; there was considerable bleeding from the gums. Six days after admission, she complained of abdominal pain of a spasmodic character. There was a certain amount of bloody diarrhea, but these symptoms disappeared within a few days. On account of the fact that there was also some blood in the urine, the child was detained in the hospital over a period of four months, by which time this condition as well as the skin lesions had entirely cleared.

The second patient was a boy, aged 13 years, who entered the surgical ward for acute colicky pains in the abdomen of seven days' duration, with vomiting and diarrhea. Four days later the purpuric rash appeared. There was considerable swelling of the left wrist. The urine contained considerable blood and albumin. In this patient, the abdominal pain persisted for approximately eighteen days. Shortly after admission there was a series of epileptiform convulsions. On discharge from the hospital, three and one-half months later, his condition was good except for a faint trace of albumin in the urine.

These cases are more or less typical of the disease as originally described. It is distinctly a malady of early life. The appearance of symptoms is variable, and the type of rash is distinctly not consistent. The abdominal symptoms are such as to be easily confused with a surgical condition. Convulsions have never before been reported, although cerebral hemorrhage is noted as a possible complication. The etiology is unknown, but Osler regarded the disease as of the angioneurotic origin. The association with urticaria and in one case with asthma, would lend support to this view.

GELSTON, San Francisco.

ISOLATED PULMONARY SCLEROSIS IN EARLY CHILDHOOD. W. LINDEN, Virchows Arch. f. path. Anat. **252**:229, 1924.

This is a report of an unusual occurrence of pulmonary sclerosis in a child, aged 1 year. At about 9 months of age the infant was first brought in for medical observation on account of a slowly developing apathy. A provisional diagnosis of a postdiphtheretic heart injury was made. After an illness of four weeks, death occurred. Necropsy revealed tremendous hypertrophy and dilatation of right side of heart. On histologic section, the pulmonary artery exhibited an unusual degree of branching and an extensive atheromatous process. The author seeks to explain the finding on the basis of congenital defects in the pulmonary veins, resulting in compensatory fibrous changes ultimately distorting the mechanical integrity of the heart itself.

SCHWARTZ, Milwaukee.

MALIGNANT NODDING SPASMS IN INFANTS. BERTA ASAL and E. MORA, Jahrb. f. Kinderh. **107**:1, 1924.

The greeting nod or "salaam spasm" is characterized by (1) the spastic nodding forward and straightening of the head with some involvement of the extremities, and later doubling over of the whole body like a tapeworm. This spell may be followed by a deep sleep; (2) this type of spasm occurred at about six months of age and changed after one year; (3) there was an organic accompaniment such as spastic paralysis of an arm or leg, or hypertonia; (4) mental disturbance is a very important point. The patients later were mentally defective or idiotic. The prognosis was always bad. Most of these are of central origin; possibly some are hysterical.

In the "lightning spasm" there is a quick jerk of the whole body as from a shock, the head and also the arms fall forward. Sometimes there is a momentary blinking. Such spasms occur singly, not in series, and are characteristic of early childhood. Therapy is ineffectual.

Spasmus nutans is benign. There is rotary movement and always nystagmus. This usually occurs in children aged from 5 months to 2 years. The development of the child is normal.

SUTHERLAND, Chicago.

EXPERIMENTS WITH PERCUTANEOUS INSULIN TREATMENT. ARVID WALLGREN, München. med. Wchnschr. **71**:10, 1924.

Experiments on a series of children, aged from 1 to 15 years, showed that insulin made into an ointment with hydrous wool fat can be absorbed from the skin and lead to a marked reduction of blood sugar.

AMBERG, Rochester, Minn.

PROTEIN THERAPY OF OBESITY. J. ST. LORANT, Wien. Arch. f. Inn. Med. **9**:341, 1924.

Protein therapy in obesity is based on two probable factors. It apparently can increase tissue function and also alter it.

The metabolism of tissue commonly has the tendency to reach some sort of physiologic equilibrium. Clinical examples of this tendency are, for example, the behavior of chronic inflammatory processes. Under the influence of protein therapy, such processes may at first show a flare up in the inflammatory condition to be rapidly succeeded by a subsidence of all active manifestation and rapid and permanent recovery.

In the atrophic infant such procedure, for example with serum injections, has resulted in weight increases quite beyond the normal. In conditions of adipositas, the reverse effect has been noted and definite and marked decreases in weight have resulted.

These peculiarly contrary effects seem to be singularly characteristic of protein therapy.

Protein substances given parenterally seem to have an additional effect, in that they augment or in some way exercise some auxiliary effect on organotherapeutic agencies, such as thyroid gland extracts. It seems that under the influence of thyroid gland extract, medication and the parenteral administration of protein the organism will store nitrogen and salts. Such storage may express itself in an increased tendency to develop edemas. A weight loss which is brought about through the use of thyroid extract, combined with parenteral administration of protein, always represents water loss and actual loss of fat.

SCHLUTZ, Minneapolis.

Nervous Diseases

EXPERIENCES AT A SPEECH CLINIC. E. W. SCRIPTURE, Practitioner **113**:381, 1924.

At a speech clinic recently held, several interesting points were brought out. Three patients with epilepsy were sent in for demonstration for the epileptic voice sign, which was discovered about fifteen years ago, when the author was making records of the voices of epileptics. The usual "flexibility" of the voice is lacking in epileptics and has never been found in any other condition, and cannot be imitated by the normal voice. Two of the patients demonstrated this very clearly, while the third appeared perfectly normal. In this case, it was found that the patient never struggled in his attacks and always fell comfortably.

Two patients with general paralysis were sent in for early speech signs. The earliest one in this disease is a variation in the established types of enunciation. The ethical sense disappears early in general paralysis, and this appears in the speech. This symptom is called asaphia and is pathognomonic. The author feels that every medical student should be trained to recognize the epileptic, the general paralytic and the multiple sclerotic voice. Hospitals should have facilities for registering speech as an aid to diagnosis. And finally, neurologists themselves should become much better versed in interpreting speech defects as indicative of disease.

GELSTON, San Francisco.

LEFT-HANDEDNESS. H. W. SIEMENS, Virchows Arch. f. path. Anat. **252**:1, 1924.

The author takes exception to the prevailing conception of the hereditary nature of left-handedness. In a group of twenty-one identical twins with left-handedness, Siemens observed that only one member in each instance exhibited the peculiarity. In three cases of identical twins, both children were left-handed. He was unable to confirm the familial tendency, ascribing former statements to this effect as faulty observations. He found definite correlation between left-handedness and speech defects. Twenty-two and one-half per cent. of left-handed subjects showed speech defects, only 6.9 per cent. of the right-handed subjects showed speech defects. He found no correlation between left-handedness and enuresis, slight relationship to epilepsy, none to deaf-mutism, color blindness and degenerative stigmas. Twins give a greater percentage of left-handedness (question of prematurity, anomalies of position, birth injuries).

SCHWARTZ, Milwaukee.

THE FATE OF HYPERIRRITABLE CHILDREN. OTTO BOSSERT, Jahrb. f. Kinderh. **106**:329, 1924.

Several authors have recently raised the question whether the hyperirritability of spasmophilia later results in defective mental development. The

author, in reviewing his cases, concludes that spasmophilia has no relation to any later mental or moral deficiency.

SOFT AND DEFECTIVE CRANIUM OF THE NEW-BORN. MICHAEL COHN, Jahrb. f. Kinderh. **106**:333, 1924.

There are three types of this condition:

1. Temporary incomplete stopping of ossification, which makes the vault soft and defective.

2. Temporary incomplete stopping of bone apposition, giving a large or persisting sagittal fontanel.

3. Complete and lasting absence of any ossification, of which the rare defect, foramina parietalia magna is an example.

The congenital soft and defective craniums of Wieland are not simple anomalies, but there may be several causative factors which give the same defect. The vault defects cannot be ascribed to enlargement of the brain in the last fetal months, with disturbed relation of brain growth and cranial ossification, but are a part of the physiologic parietal fissure.

SUTHERLAND, Chicago.

EPILEPTIFORM CONVULSIONS IN LEAD POISONING. RIMPEI WAKAO, J. Pediat. (Tokyo) **293**:1362 (Oct.) 1924.

The author reports a case of a girl, aged 5 years, who came with the complaint of an oncoming attack of epilepsy which she had had before. These attacks were all preceded by constipation, with general malaise, loss of sleep, accompanied by vomiting and green stool. There was always a slight rise in temperature. An older child of the same family died in a similar attack one year previously. Examination revealed a pale child of normal nutrition, with slightly dilated pupils. The gums were normal but the front teeth were discolored gray to brown except at tips. Blood examination revealed from 6 to 8 erythrocytes with basophilic degeneration. The mother complained of slight numbness of extremities and her blood smear also showed stippling of erythrocytes. In arriving at diagnosis, it is interesting to note the fact that the family of the patient is engaged in the manufacture of white toilet powder whose base is lead in some form. The author tested a sample of the powder and found a strong reaction for lead. It is also said that the atmosphere of the house is filled with white lead powder which is constantly inhaled.

KATO, Los Angeles.

Diseases of the Eye

RETINAL HEMORRHAGES IN THE NEW-BORN. MAX W. JACOBS, J. A. M. A. **83**: 1641 (Nov. 22) 1924.

Jacobs examined 190 infants shortly after birth to note injuries and anomalies. The pupils were dilated with 0.1 per cent. atropin solution, and the examination made with the electric ophthalmoscope by the direct method. A pacifier was given to each infant to facilitate the examination. One hundred and fifty-seven babies were examined in the first twenty-four hours and thirty-three after the first day of life. All babies had received prophylaxis by the method of Crede.

In five cases the cornea was found to be steamy. One baby had persistent pupillary membrane. The vitreous was never found abnormal. Paralysis of an extrinsic muscle was not found. Nystagmus was noted in one case but disappeared in a few days. The retinal veins were frequently increased in caliber, and the optic nerve heads blue gray. Four showed retinal hemorrhages in twenty-two examined before 6 hours old, seven in thirty-four between

6 and 12 hours, seven in fifty-five between 12 and 18 hours, one in forty-six between 18 and 24 hours and four in thirty-three after the first day of life.

Hemorrhages were never present when the Wassermann test was positive. In the series of 157 cases, labor was induced nine times and four of these babies had retinal hemorrhages. Thirty-three per cent. of the children having hemorrhages were born of mothers less than 25 years old, while in 68 per cent. the mothers were over 25 years old. Thirty-six per cent. were primiparas and 64 per cent. multiparas. Twenty-one per cent. were colored children and 79 per cent. white. Forty-two per cent. were born with the aid of forceps. The clotting time was taken whenever retinal hemorrhages were noted but it never exceeded eight minutes.

WESCOTT, Chicago.

Diseases of the Skin

THE CUTANEOUS REACTION IN ALLERGIC DISEASES OF INFANCY AND CHILDHOOD. W. RAY SHANNON, Arch. Pediat. **41**:834, 1924.

It is contended that in the interpretation of the cutaneous protein test in infancy and childhood, an erythema must be considered as the indication of a positive sensitization. Five striking cases are cited in which no results would have been possible had not such an interpretation been made. Further support for this contention is found in the fact that an erythema may frequently be demonstrated to precede a wheal type of reaction in an increasing sensitization, and in that it may also often be shown to follow a wheal in a decreasing sensitization. It is common for the tissues of the allergic person to react to irritative phenomena in a magnified manner. As a result, it is not uncommon to find some erythema persisting around all of the tests. This does not disprove the original contention, as satisfactory clinical results can frequently be obtained with therapy based on the most marked reactions. It does, however, demonstrate the fact that the interpretation of the positive reaction is a relative thing, dependent on the particular reactivity of the tissues of the person concerned at the time.

VON MEYSENBUG, New Orleans.

ECZEMAS OF INFANCY AND CHILDHOOD. GERSHOM CLOSSON, Northwest Med. **23**: 572, 1924.

Closson divides eczemas into a more frequently occurring group, easily amenable to treatment, and a less frequent chronic group which is very resistant to treatment. He believes most eczemas arise from an internal or metabolic cause, and stresses the importance of a proper diet. He finds fat indigestion most often associated with a moist eczema, and starch indigestion with the dry forms. He comments on the superiority of ointments of crude coal tar after the formula of White over former methods of local treatment.

SCOTT, Philadelphia.

URINALYSIS AND METABOLISM IN A CHILD WITH SCLERODERMA. JIRO OKUNI, J. Pediat. (Tokyo) **293**:1281 (Oct.) 1924.

Okuni studied the distribution of nitrogen in the urine and the metabolism of nitrogen, sodium chlorid, phosphorus, calcium and magnesium in a girl, aged 12 years and 1 month, who entered the University Hospital at Kyoto with the complaint of stiffness of both forearms and thighs and slight redness and swelling of lower eyelids and cheeks. The examination was made at two periods, the last of which was preceded by administration of a thyroid preparation, which, however, never exceeded 0.105 gm. His observations were as follows: (1) There was no sudden change from positive to negative nitrogen exchange; (2) ammonia excretion was in direct proportion to the total nitro-

gen but its percentage was high, ranging between 6.23 and 9.45; (3) urea excretion was also in direct proportion but its percentage was low, 66.3 to 75.2; (4) changes in both ammonia and urea excretion were due to the impaired function of urea formation in the liver and not to the amount of urea in the body; (5) uric acid and the purine bodies were decreased in the urine; (6) the excretion of amino-acids was within the normal limits; (7) creatinin excretion was greatly decreased and the percentage of its nitrogen to the total nitrogen as well as the creatinin number was markedly low; (8) creatin excretion was high for the age of the child and its percentage with reference to the total nitrogen was also high; (9) total creatinin excretion and the percentage of its nitrogen to the total nitrogen was normal or slightly high; (10) the percentage of creatin with reference to creatinin was very high and the amount of creatin far exceeded that of creatinin; (11) judging from the excretion of creatin and creatinin, there is no thyroid deficiency in scleroderma; (12) the exchange of sodium chlorid depended on the amount of ingested salt but it was positive throughout; (13) phosphorus metabolism was constantly positive; (14) calcium metabolism depended also on the ingested food, but its amount in the urine was reduced; (15) magnesium metabolism was always positive, but the amount was low; (16) the relation of sulphur to the total urinary nitrogen was normal; (17) the sulphur in ethereal sulphates and its percentage with reference to the total sulphates was inconstant; (18) phosphorus was normal or slightly low; (19) urinary magnesium was low as compared with urinary calcium, the amount being 3.88 to 16.6; (20) the proportion of urinary phosphorus to calcium was in general reduced.

KATO, Los Angeles.

Surgery and Orthopedics

DENUCE'S METHOD OF REDUCTION OF CONGENITAL DISLOCATION OF THE HIP, WITH REPORT OF CASES. HERBERT E. COE, Northwest Med. **23**:569 (Dec.) 1924.

Coe gives a history and a description of the technic of Denuce's method of reduction, and describes patients of his own treated in this manner with gratifying results.

SCOTT, Philadelphia.

THE TREATMENT OF STAPHYLOCOCCUS AND STREPTOCOCCUS MENINGITIS BY CONTINUOUS DRAINAGE OF THE CISTERNA MAGNA. WALTER E. DANDY, Surg., Gynec. & Obst. **39**:760 (Dec.) 1924.

Since Victor Horsley's unsuccessful effort in 1890, three types of surgical treatment have been applied to meningitis of pyogenic origin (1) repeated lumbar punctures; (2) continuous drainage from the spinal canal, cisterna magna, the pontine cisterna, the lateral ventricles and the subarachnoid space in the parietal region; (3) irrigations of the subarachnoid space by blood or antiseptic solutions. None of these methods have resulted in any marked decrease in the mortality. The two favorite sites for cerebrospinal drainage are the lumbar spinal canal and the cisterna magna. The cerebrospinal fluid circulates in a closed system of spaces. The interior or ventricular part of the system is concerned with the formation of cerebrospinal fluid, the exterior or subarachnoid part is concerned with the absorption of the fluid. Communication between them is solely through the paired foramina of Luschka and the mesial foramen of Magendie, therefore their patency is essential to life. The subarachnoidal portion may be compared to a tree, the cisterna magna being the trunk and the branches represented by the radiating network of channels and pools which cover the surface of the cerebrum and cerebellum. Normally there is a very free communication between all parts of the sub-

arachnoid space, as has been shown experimentally with various dyes. Under abnormal conditions, however, the possibility of drainage of this system of channels will depend on the degree of changes in the character of the spinal fluid.

The operative procedure employed by the author is as follows: Midline incision over the occiput exposing upper cervical vertebrae. A circular area of occipital bone 2.5 cm. in diameter is removed, including the posterior arch of the foramen magnum. The dura is opened along the midline and occipital sinus ligated. This opening is enlarged laterally as needed. The arachnoid is opened widely and cerebrospinal fluid allowed to escape. The funnel end of a small catheter is sewn to the edges of the dura. The trapezius muscles and skin are loosely brought together, so that fluid may easily leak out if the tube becomes obstructed. After removing the tube about the fourth or seventh day, the wound is allowed to close itself.

Four cases have been thus treated:

Case 1.—A boy, aged 6 years, suffered a basal skull fracture in an automobile accident. Within two days he developed meningitis due to the hemolytic streptococcus. Within thirty-six hours the cisterna magna was drained and fluids forced by mouth. The tube was removed on the seventh day. The temperature began to subside after the fourth day and returned to normal nine days after operation. Recovery was uneventful.

Case 2.—A boy, aged 11 years, developed a staphylococcus meningitis following lumbar puncture. On the fifth day the cisterna magna was drained and the tube was removed five days later. The temperature reached normal fourteen days after operation and remained there. Recovery was uneventful.

Case 3.—A woman, aged 36, developed a streptococcus hemolyticus meningitis eighteen hours after removal of a tumor of the cerebellopontine angle. The cisterna magna was drained thirty-six hours after the onset. Death ensued within twenty-four hours.

Case 4.—A woman, aged 49, developed a streptococcus viridans meningitis after removal of a cerebellopontine angle tumor. The cisterna magna was drained on the eighteenth day and continued four days. After removal of the tube, fluid was repeatedly aspirated from the lateral ventricles and spinal canal. The temperature did not begin to subside until forty-three days later but the patient made a complete recovery.

Miller, Chicago.

Two Cases of Chronic Invagination. Koichi Yamagishi, J. Pediat. (Tokyo) **293**:1372 (Oct.) 1924.

Yamagishi reports two cases of chronic invagination in a boy, aged 3½ years, and in a girl aged 7 years and 9 months, respectively. In the first case, the characteristic sign was the constant presence of a large tumor mass in the right iliac fossa, which on operation was found to be made up of descending invagination of the small intestine into the first portion of the ascending colon, which was caught in the ileocecal valve and incarcerated. There was also an ascending invagination of the distal portion of the ascending colon and the proximal portion of the transverse colon. The postoperative condition was satisfactory and recurrence was not noted. In the second case the patient was kept under observation for two months in the hospital, during which time the treatment consisted in the regulation of diet, use of belladonna and electric massage. Under this management the condition of the patient steadily improved, but the tumor mass in the right iliac fossa was persistent. On the operating table the mass was discovered to be an invagination of the colon. The author adds that in chronic intussusception the symptoms are far less marked than in the acute cases, and the operative treatment may be postponed without much damage to the general condition of the patient.

Kato, Los Angeles.

Miscellaneous

ASTHENIC CHILDREN. ISAAC A. ABT, South. M. J. **18**:19, 1925.

The author presents, in a brief review, the prevalent ideas concerning the symptom complex present in children having the so-called asthenic constitution. The tendency in modern medicine is to regard the asthenic habitus as based on constitutional defects, namely, on certain properties transmitted from the germ plasm.

No specific medicinal treatment can be indorsed for this type of person. The only beneficial treatment is to harden these children by proper training. Increase in fat is not so much to be desired as an increase in the tonus of the musculature, which, in turn, improves the heart and digestive organs.

SCHLUTZ, Minneapolis.

Society Transactions

NEW ENGLAND PEDIATRIC SOCIETY

Boston, Mass., Nov. 14, 1924

RICHARD SMITH, M.D., *President*

THE COMPARATIVE COMPOSITION OF INFANT FEEDINGS EXPRESSED IN PERCENTAGES OF TOTAL CALORIES. Presented by DR. GROVER POWERS.

The constitution of a great variety of infant feeding mixtures has been expressed in terms of the percentage which each energy producing component is of the total caloric value of the food mixture. This method of food dissection has been the means of extricating the feedings from a maze of metabolically meaningless quantitative relationships, and made them available for comparative study. Stripped of encumbering nomenclature, the foods have been set forth on a significant basis in terms of the standard unit of nutritional currency, the calorie. On this basis, a host of apparently dissimilar mixtures have lost an artificial individuality and have been classified as members of six distinctive groups. Here individual differences may be studied where they actually exist, that is, in mineral content, chemical and biologic values of protein, carbohydrate and fat, degree of denaturization and water content.

NEWER POINTS OF VIEW IN INFANT FEEDING. Presented by DR. EDWARDS A. PARK.

DR. PARK summarized the ideas of Finkelstein and his school, and contrasted them with those of other schools which previously had emphasized the value of the examination of stools in infant feeding. He drew attention to the fact that diarrhea does not necessarily denote indigestion and discussed concentrated feeding versus dilute feeding. Vomiting, he felt, is more often the result of mechanical conditions than of indigestion, and that the secret of successful treatment of vomiting in the great majority of instances is to give small quantities of concentrated food at frequent intervals. He uses concentrated foods made from undiluted sour milk in the New Haven clinic and warned against the use of over-diluted milk.

Many infants, and especially premature infants, thrive best when they receive from 150 to 200 calories per kilogram of body weight. This is often also true of atrophic infants. Two hundred calories per kilogram representing the upper limit of caloric requirements. Harm can be done by overfeeding. In the case of most malnourished infants, it is not necessary to give more than 150 calories per kilogram and many infants do better on concentrated foods at short intervals than they do on dilute formulas at long intervals. Premature, feeble and vomiting infants will first begin to thrive when the interval is shortened to two hours or less. Cane sugar is probably an equal of any sugar for infant feeding. Two sugars are perhaps superior to a single sugar. A sugar and dextrin are perhaps superior to a single sugar. Sugar and flour in combination are probably superior to a single sugar. Flour or cereal mixtures are well tolerated by most infants. Many atrophic, feeble and premature infants will not gain until the carbohydrate in the feeding has been increased to 14 or 15 grams per hundred cubic centimeters of milk.

If an infant cannot live for part of a day in sunlight, cod liver oil should always be added to the diet. By the end of the first month an infant should receive from one to one and a half teaspoonfuls of cod liver oil daily, and by the end of the second month two to three teaspoonfuls daily. Cod liver oil is to be regarded merely as a substitute for radiant energy. Probably from 80 to 90 per cent. of the difficult feeding cases in hospitals are in infants with infections. For most infants it can be said that the protein in cow's milk mixtures should comprise from 10 to 20 per cent. of the calories, the carbohydrate from 50 to 70 per cent. and fat from 20 to 40 per cent. Breast milk is the best food under almost all conditions, but in infants with severe diarrhea, breast milk may add to the diarrhea or aggravate the condition.

DISCUSSION

DR. BLACKFAN: There is one point which has not been especially emphasized in the feeding of infants, and that is the very great individuality of groups of infants. The problems met in the homes of the well-to-do are much less acute than those seen in clinics. I wonder if it is fair for us to accept all the recommendations regarding the feeding of infants which are discovered in large hospital pediatric clinics.

Dr. Powers said that lactic acid milk is fed because it is easily digested and assimilated. I think we ought to keep this in mind. I think we are fortunate in having both Dr. Powers and Dr. Park here tonight and think that they have given us a lot to think about.

DR. TALBOT: Attention is drawn to the fact that the rationale of the caloric requirements of children of different ages and weights is based on basal matabolism. This shows that a child who is malnourished, while requiring approximately the same number of calories as a child of the same weight, requires a great many more calories per kilogram of body weight than does the child of average or normal weight.

DR. SISSON: I notice that Dr. Powers did not refer at any time to the value of salts in the mixture. It seems that this also ought to be taken into consideration. Our experience in feeding babies at the Boston Lying-In Hospital was that breast milk could not be looked on as the most desirable food for premature infants, but we have not found anything that is better. We see a great many infants who do not thrive even on breast milk containing the sufficient caloric needs. They do not gain, and develop so-called rickets in spite of the addition of cod liver oil to the feeding, in amounts as great as from 2½ to 3 teaspoonfuls a day. We are adding dry milk powder to breast milk and giving it to babies only a few weeks of age and they gain rapidly. Premature babies will gain on 50 to 60 calories per pound and I do not think that 100 calories per pound is necessary.

ST. LOUIS PEDIATRIC SOCIETY

Dec. 19, 1924.

GEORGE M. TUTTLE, M.D., *President*

REPORT OF TWO CASES OF PYELOCYSTITIS IN BOY BABIES IN THE FIRST WEEK OF LIFE, WITH OBSTRUCTION OF URETER AND MULTIPLE ABSCESS OF KIDNEY IN ONE. Presented by DR. T. WISTAR WHITE.

M., a large, full term, breast-fed boy, progressed normally until the seventh day when he showed marked depression but no pain, followed by fever due

to colon bacilli and pus in the urine. Though only the initial febrile attack occurred, the condition was peculiarly resistant. The urinary findings have remained the same for nearly a year.

I., a small, slightly premature boy, developed fever on the sixth day. Several days later great pain was evident and he refused to nurse. When 10 days old the temperature was 104 F. The urine contained colon bacilli and an unusual amount of pus. The infant cried continually. The abdomen was resistant, sensitive and distended. Laparotomy was considered. The usual remedies gave no relief, and the child died when 19 days old. Necropsy showed no abdominal changes. Both kidneys were enlarged and contained pus. The left ureter was dilated to the size of one's finger, until just before entering the bladder when it narrowed and was completely obstructed. The left kidney contained a number of abscesses. The obstruction was probably congenital.

UNDESCENDED TESTICLE: HYDROCELE. Presented by DR. DALTON K. ROSE.

In consideration of undescended testicle and in some instances of hydrocele, one finds the etiology in maldevelopment. (The normal development and descent of the testis were then discussed in detail.) In cryptorchid animals, interstitial cells show an increase, the sexual and sustentacular cells a decrease, the latter a fatty accumulation and either a fatty degeneration or fibrosis of the whole organ.

The descent should be complete a few months after birth, although it has been made as late as the fourteenth year.

The age of choice for operation is after the third year and not later than the fifth or sixth. Fatty degeneration has been observed in the second year, but to a moderate degree. Generally speaking, testicles in malposition are not always sterile. Ectopic testicles follow one of the lower ramifications of the gubernaculum, or may be reflected under the abdominal wall.

Factors in undescent are a short spermatic cord, due to a binding together by fibrous tissues of tortuous vessels, causing relative shortening; absolute shortness of vessels or vas; malformation of the gubernaculum, or inguinal canals; enlarged testis or epididymis; long mesorchium; imperfect action or formation of the cremasteric muscle; adhesions to peritoneum, the wearing of trusses, or, herniotomy in infancy. Deficient blood supply in undescended testicle, pressure or trauma may account for its degeneration and may play a part in tumor formation.

The operation of choice was devised by Dr. Bevan and consists usually in separating the vessels within the cord by blunt dissection of the fibrous tissue bands. The operation has several modifications, but in itself saves a viable testicle, insures its fixation within the scrotum and repairs the accompanying hernia. It is an absolute essential not to cut the vessels of the cord, for in too large a percentage atrophy results.

Hydrocele in the congenital, infantile or inguinal type is associated both with hernia and undescended testicle, the three being varieties of nonclosure or imperfect closure of the processus vaginalis. Idiopathic hydrocele may be persistent, symptomatic or acute; they are secondary to trauma, parasitic infection, sexual excess, etc. They may or may not be encysted due to adhesions within the tunica vaginalis, or within the cord, due to intermittent closure of the processus funicularis.

The fluid may be clear, fibrinous, hemorrhagic or purulent. When clear, it suggests an exudate rather than a transudate. Preponderance of mononuclear cells suggests tuberculosis, and the presence of spermatozoa and cholesterin crystals, an open seminiferous tubule.

Diagnosis is made by the symptoms: typical pear shape, fluctuation, transmitted light and the position of the testicle which is usually posterior. The

surgical treatment consists of tapping; injection of an irritant, such as iodin or carbolic acid, and open surgery, excision and eversion of the sac giving the best results.

PYELOCYSTITIS: MEDICAL TREATMENT. Presented by DR. PARK J. WHITE.

Modes of infection of the kidney pelves were discussed in detail in the light of the work of Helmholz and others, with especial emphasis on hematogenous infection because of the frequency with which pyelocystitis follows focal infection elsewhere in the body. The importance of removing such foci, and of dietetic and other measures directed at the general health of the patient, was brought out. The work of Shohl and Deming, Marshall, and others, was cited as evidence to disprove the idea that either hexamethylamin or alkali can be given in dosage sufficient to diminish the growth of colon bacilli, except in cases where there is stasis. The beneficial effect of alkali is due to the substitution of nonirritating urine, for the previously irritating acid urine, to diuresis, and to increased phagocytosis. It is thus rational and desirable to force liquids in patients receiving alkali therapy; but irrational to do so in those receiving hexamethylenamin. Indeed the increase in liquid intake and output is probably the most efficacious single therapeutic agent. Because of difference in immunologic reactions in the urine and in the blood, vaccine and serum therapy can hardly be considered to be on a scientific basis.

PYELOCYSTITIS: SURGICAL TREATMENT. Presented by DR. DALTON K. ROSE.

Surgical treatment is based on determination of type of pyelonephritis with cystitis: a hematogenous infection, contamination from neighboring organs or ascending infection. In the latter it is likely to be associated with some obstruction to the urinary flow, although it may be via the lymphatics. The colon group of infection is first in point of frequency and the cocci next, with proteus, pyocyaneus, pneumococcus, and so forth following. Especially in children and young adults, the most important point to determine is why did the organism linger long enough in the kidney to multiply, as all normal kidneys secrete, and do not harbor, organisms in health. This implies some obstruction to urinary flow. Search is made for anomalous kidney pelves, ureters, bladder, posterior urethra and urethral meatus, and for such pathologic conditions as cystic kidney either multiple or single, tumor, stone, stricture or malposition of kidney.

Given a slight interference in outflow, the excreted organism lingers, multiplies, and through edema and increased spasm of the ureter from ureteropelvic to ureterocystic junction, tends to retard the outflow and so increase the kidney residual. These facts may start the vicious circle which can terminate in a pyonephrosis.

The greater the malformation or other factor influencing stagnation, the earlier in life is the infection likely to be precipitated. This fact is borne out by the large percentage of pyelonephritis seen in young adults having as their anatomic factor a simple bifid pelvis. In any persistent type of infected kidneys in infants, we expect to meet a greater degree of malformation or definite pathology and for this reason, cystoscopic examination should be carried through exactly as in adults, including urethral catheterization, separate urine determination, functional test, ureterograms and pyelograms. It is advisable, however, to examine only one kidney at a time and that one only when the blood nitrogen retention is as low as it can be brought.

Pyelitis always means a nephritis and usually a perinephritis and ureteritis. For this reason organisms linger long after subjective symptoms have disappeared. A purulent perinephritis requires drainage, possibly a secondary nephrectomy, depending on the destruction of kidney tissue and the condition of its fellow. Nephrostomy in pyelonephritis is generally indicated when the ureteral block is absolute, either through kink, spasm, pressure, stone, tumor or stricture, the wound closing after relief of obstruction.

Nephrectomy is indicated in unilateral tuberculous pyelonephritis, or in hydronephrosis or pyonephrosis, in the latter only if the opposite pelvis is normal and uninfected, without subjective symptoms from a dilated kidney. Repeated lavage, especially with indwelling ureteral catheters will frequently overcome the infection sufficiently to reduce edema and allow satisfactory drainage of the kidney pelvis. Ureteral strictures must be cut or dilated; contracted bladder necks frequently require an open operation, and any malformation, foreign body or pathologic condition calls for the same procedure as indicated in themselves, remembering that a nephrostomy wound is slow to close if any lower obstruction remains.

Blood transfusion and intravenous injection of neutral acriflavine, mercurochrome-220 soluble or gentian violet may be indicated at times.

CENTRAL STATES PEDIATRIC SOCIETY

Minneapolis, Oct. 31, 1924
Fourth Session

E. J. Huenekens, M.D., *President*

Experimental Work on Treatment of Poison Ivy Dermatitis. Presented by Dr. E. D. Brown.

During experimental work with the plant, the poison was applied to a group of students as well as to himself, applying it to four different areas on the arm and treating the resulting dermatitis with different remedies. Among the group were lead acetate, potassium permanganate, fluid extract of grindelia and various agents which produced an irritant action, such as Labarraque's solution, ammonia water, formaldehyd, bromin and tincture of iodin. As a rule, the irritants lessened the discomfort and hastened resolution better than the astringents. Following this experimental work, a series of cases has been treated with a solution composed of potassium hydrate 5.0, liquor cresolis compound 5.0, and water to make 100 c.c., with gratifying results. It is applied once or twice a day after rupturing the vesicles, if present, by rubbing with a piece of gauze. This treatment apparently shortens the duration and relieves the itching.

Differential Diagnosis Between Lymphatic Reaction and Lymphatic Leukemia from a Cytological Standpoint. Presented by Dr. Hal Downey.

Acute lymphatic leukemia is differentiated from lymphatic reaction by the large number of immature cells. Distinction between lymphatic reaction and chronic lymphatic leukemia may have to depend on clinical findings and history, because in the chronic lymphatic leukemia there may be few immature cells. Chronic lymphatic leukemia is probably never seen in children.

Effects of Inanition and Malnutrition on Growth and Structure. Presented by Dr. C. M. Jackson.

This work has been chiefly experimental and on the lower animals, but incidentally a considerable amount of data has been collected on the effects in human beings, particularly the effects of organ weights and body weights in children. In the lower animals we can control the influencing factors better. Each organ seems to have a growth curve of its own, and because the body is emaciated it is not correct to estimate that all the organs will be stopped in their growth. On the contrary they may attain a larger size than usual. The organs have been divided into three groups. (1) Brain and skeleton; these lose practically nothing during inanition. (2) Thymus

and lymph organs; these lose heavily during inanition. (3) An intermediate group, some losing more and some less between the two extremes. There is a general agreement between the findings in animals and man, but in some instances there is a marked difference, the suprarenal representing one of them.

DETOXIFICATION OF BACTERIAL TOXINS WITHOUT ALTERING ANTIGENIC PROPERTIES. Presented by DR. W. P. LARSON.

In studying the effects of the surface tension on pathogenic bacteria, it was found that practically all lost their virulence if placed in a solution of low surface tension. A solution of castor oil soap, which is readily soluble, was used. Its effect was tested on various toxins, and it was found that diphtheria and tetanus toxins are neutralized if mixed with castor oil soap. The next question was to determine whether such detoxicated toxin will immunize. Rabbits and guinea-pigs were treated and large quantities of antitoxin were found piled up in their blood serum, showing that this is an excellent antigen. There is an objection to using the toxin to neutralize the antitoxin, and by using the soap in place of the antitoxin an effective detoxication of the toxin is obtained, which yet retains its immunizing value. In the cases of tetanus toxin if it is neutralized with soap and injected into a guinea-pig there is no intoxication. If the toxin is partially neutralized and injected into the leg of a guinea-pig it may develop tetanus, but the animal always recovers, although recovery never takes place when given a toxin that has not been neutralized. The same is true with rabbits. Botulism toxin is more resistant to the soap than are the other two toxins.

SPEECH DEFECTS IN CHILDHOOD. Presented by DR. SMILEY BLANTON.

A simple classification of speech disorders which is descriptive and helps to carry in mind these disorders is given.

The first mentioned is delayed speech, probably due in most instances to a defective nervous system, sometimes to injury at birth.

Second, oral inactivity, inactivity of the speech organs. One fundamental cause of this is believed to be rickets. In nearly every case there is defective nutrition which has affected the tongue, so that the child cannot make the proper sounds. In some, no cause could be found for the speech defect, and a third cause for this oral inactivity is the fact that the child gets what it wants without talking properly.

The third is sound substitution, or lisping, and very few of these conditions are due to any malocclusion or difficulty with the speech organs. This condition may be due to imitation of the child's elders or because it ties a child to infancy.

The fourth is stuttering and stammering, not a disease but a symptom in most cases, due to mental conflict.

Speech disorders should be carefully considered by the medical profession. For many years they have been in the hands of nonmedical people, where there is no scientific knowledge and inadequate treatment. If a child has not good speech at 2 or 3 years of age, he should be considered by the physician as having something wrong physically or psychologically.

INTRACRANIAL INJURY AND HEMORRHAGE IN STILLBORN AND NEW-BORN INFANTS. Presented by DRS. F. L. ADAIR and W. A. O'BRIEN.

DR. W. A. O'BRIEN: In this series of 300 necropsies, 60 per cent. were stillborn and 40 per cent. neonatal and new-born, and 26 per cent. died before labor started. In the intrapartum group, dying during delivery, are 19 per cent.; in the postpartum group, the babies born with heart beat but respiration not established, 15 per cent. Dying the first day 22 per cent., second day 14 per cent., third day 18 per cent. and so on, half as many dying on the second day as all the rest of the time.

The cause of intracranial hemorrhage we have ascribed to trauma, asphyxiation and hemorrhagic disease. The terms subtentorial and supratentorial do not describe the process. In opening the head of the baby they use the Beneke technic. The statistics from this technic and the others should not be compared. The scalp is split just as for any other necropsy, and the front and back are pulled down, which exposes the side of the skull, then the parietal bones are cut and pulled back; the surface of the brain is looked over and the presence of hemorrhage is noted. Then instead of cutting the tentorium and taking out half, the whole area is examined. Under the old technic the tentorium was not examined and it is believed that the tentorium is the key to many of the intracranial hemorrhages seen today. By this method the tentorium and the falx in position are seen.

Almost every baby's head shows a large number of hemorrhages, either of the scalp or elsewhere. One type is the cephalohematoma and there are two examples of that, both causing symptoms of paralysis. A second type of hemorrhage is the diffuse hemorrhage throughout the pia-arachnoid, where it is seen all over the surface. It is very difficult in some cases to recognize that hemorrhage from a surface coating of the pia-arachnoid with spinal fluid. The third type is the so-called ventricular hematoma which comes in premature infants, and perhaps the only thing that can be said against this method of opening the head is that this is frequently destroyed. The fourth type is the ordinary hemorrhage. Fifth is the hemorrhage of the brain substance, which is not a very common variety. The sixth type is the so-called hemorrhage of the dural folds, where the blood is present in the cavity, is usually fluid and seldom in large clots. In opening the head in this way, it was opened after the body was examined and so the blood had gone from the sinuses.

Stillborn infants never show hemorrhage unless they occur as the labor starts. In one series where the baby died in utero a few small hemorrhages were found, assumed to be due to asphyxiation. The intrapartum group was composed of stillborn and term infants. Of the stillbirths there were 60 per cent. hemorrhage and in the term infants 70 per cent.

In looking for the source of hemorrhage, the most obvious symptom is trauma and most of the deaths are due to trauma during labor. Tears are found in the tentorium, and the fibers will be pulled apart. The hemorrhages are classified as to whether or not a tear in the tentorium is present.

Hemorrhages due to trauma are present in 92 per cent. postpartum; due to other causes only 8 per cent., and of the trauma group 60 per cent. showed tears.

In the postpartum group that died without ever getting respiration started, 18 per cent. showed hemorrhage, and of these there was 25 per cent. with tears and 75 per cent. without.

In the full term group 88 per cent. showed hemorrhage; of these 86 per cent. showed tears and only 7 per cent. showed hemorrhage.

Of the full term infants that died postpartum, 90 per cent. showed hemorrhage. The first day babies in the premature group (49 premature infants) 57 per cent. showed hemorrhage; 43 per cent. hemorrhage only in the folds, and 25 per cent. showed tears. In the term group 73 per cent. showed hemorrhage the first day.

After the first day in a small group that lived and showed hemorrhage, 31 per cent. had tears and 54 per cent. hemorrhage, giving a total of 85 per cent. traumatic hemorrhage. In the term infants, 67 per cent. showed tears and 11 per cent. hemorrhage of the dural folds.

Checking over the presence of blood either in the cerebrospinal fluid, in the pia-arachnoid, or in the ventricles of the brain, showed trauma in 91.9 per cent. of all infants from intra-uterine life to fourteen days postnatal. In other infants where the dura was not torn, 55 per cent. showed tears and 45 per cent. showed hemorrhage.

Summing up, in an examination of 300 babies, a total of 90 per cent. hemorrhage was found, which could be ascribed definitely to trauma.

A specimen of the largest hemorrhage found, and the head of a premature infant showing a tear in the tentorium on the right were presented.

Dr. F. L. Adair: The prevention of intracranial hemorrhage is largely an obstetric problem. The obstetric injury may be the cause of the hemorrhage but not the cause of death in many instances. The term which has been used regarding the intracranial hemorrhage is cranial stress. During delivery, the head is subjected to generalized compression and then to molding; there is also a pressure below, the contractions of the uterus above forcing the spine against the base of the skull. Conclusions cannot be drawn, except as applying to necropsy material. Hemorrhage without laceration, hemorrhage with laceration and laceration without hemorrhage have been found.

The diagnosis is important from the standpoint of treatment, and an accurate history of the labor is of great importance in this connection. So-called normal labors quite frequently are associated with evidence of both hemorrhage and laceration. In connection with the short, violent labors and also with prolonged labors, definite evidence of injury has been found, with laceration and hemorrhage in both, and the babies usually die neonatal deaths. It is felt that the symptoms which commonly point toward intracranial hemorrhage point rather to brain irritation, which might result from a variety of different causes.

In the necropsy material, little evidence of hemorrhagic disease as the cause of intracranial hemorrhage was found. This may have been due to the fact that whole blood is used so frequently in the new-born. There has been direct evidence of trauma in practically all of the cases. The babies that have died neonatal deaths must have had normal clotting and coagulation time.

Spontaneous labors produce intracranial hemorrhage and laceration, and in some instances the manipulation has been blamed when it was not the real cause of the fatal outcome.

Book Reviews

THE ADVANCE OF ORTHOPEDIC SURGERY. By A. H. TUBBY. H. K. Lewis & Company, London, England.

Mr. Tubby, in a splendid little volume of about one hundred fifty pages, reviews the most notable advances in orthopedic surgery since the last edition of his textbook on orthopedic surgery, entitled: "Deformities and Diseases of Bones and Joints," published in 1912.

Among the advances made which he discusses are:

1. The simplification of many orthopedic problems by the use of radiology, enabling us to recognize features of deformities and diseases which previously had been unfamiliar.

2. The more exact knowledge of the course anatomy of large nerve trunks, contributing to the advance of nerve surgery.

3. The close pursuit of morbid anatomy and histology, teaching us the nature of the muscle and nerve changes in such conditions as Volkmann's ischemic paralysis, congenital torticollis and various bone growths.

4. Bacteriology has thrown light on the problem of anterior poliomyelitis, establishing its contagious nature.

5. By the careful study of normal and abnormal postures, the effect of continued mal-position on the functions of the internal organs has been learned.

6. The nation-wide awakening to the responsibility for the welfare of cripples.

7. The values of recreative and reconstructive surgery and physical (?) treatment of orthopedic deformities.

This valuable text is characteristic of Mr. Tubby's other works, being filled with interesting metaphors, as in speaking of the advance of orthopedic surgery, he says: "It possesses certain characteristics wherein it differs from an army in the field. There are no halts. Orthopedic surgery has not marked time; it has gone from strength to strength and, unlike a conquering army, its man power has not wasted, but has grown stronger and more numerous as each obstacle has been surmounted."

THE PRACTICAL MEDICINE SERIES. VOL. 3. THE EYE, EAR, NOSE AND THROAT. Edited by C. L. Mix, M.D., editor in chief; Casey A. Wood, C.M., M.D.; C. P. Small, M.D.; Albert H. Andrews, M.D., and G. E. Shambaugh, M.D. Price, $2.00. Chicago: The Year Book Publishers, 1924.

This volume, while of interest to the specialist in this line, is of value to all practitioners whatever their especial field. The authors have made no effort to present a textbook. Instead, the presentation is a medical digest covering the work and thought of the world during the last year. Consequently, the reader is expected to bring to its pages a comprehensive knowledge of the basic information about which this book is written. At the same time its material is presented in a manner so clear and so simply worded, that the undergraduate or the practitioner formerly uninterested will find it readily intelligible. In every case, full credit is given to the author and to the journal in which his work appeared. The value of every article is greatly enhanced by the interpolated explanations or criticisms of the editors. Much attention is given to focal infections; their recognition and treatment, and to the promise of prophylaxis and of immunity which their study offers. While strictly practical in nature, space has been utilized for a little day dreaming now and then concerning the unlimited possibilities of medicine of tomorrow. This book is seriously recommended to all students of medicine, whatever their specialization.

LES DYSTROPHIES DE L'ADOLESCENCE. By V. HUTINEL, Paris, 1924.

Few clinicians can discuss this subject with the authority of Hutinel, who began his studies shortly after relieving Grancher in 1889, at the Clinique des Enfants-Malades. His isolated reports have finally been assembled into a volume of 232 pages, with 15 illustrations, and an earnest attempt has been made to classify these disorders, particularly in the light of recent investigations of the rôle of the ductless glands.

Hutinel cleverly contrasts the formulative or evolutionary dystrophies of early life with the regressive types seen in old age; in an early chapter, dedicated to the anomalies produced through hormonic disequilibrium, he stresses the clinical pictures in succession of thyroid, hypophyseal, suprarenal and genital deviations; in another chapter are "passed in review" the syndromes of the pluriglandular dystrophies, notably those of infantilism, obesity, "la maigreur," dwarfism, gigantism, and, unusual as it may seem to American readers, chlorosis, which Hutinel regards as something infinitely more complex than a simple anemia, and closely associated with the genital function. Until something more concrete is offered, he would class chlorosis among the ovarian dysplasias.

Further divisions of this valuable work are devoted to the analysis of those disorders which have an essential basis in perverted glandular activity, yet whose clinical characteristics are modified by coincident alterations in the vagosympathetic system. Among these he includes osseous deformities, such as those of late rickets, cardiopathies and other departures from the normal in the circulatory apparatus, certain disorders of the urinary and digestive systems. The importance of differentiating true dystrophies from hereditary syphilis is here strongly emphasized. The work is concluded by a most comprehensive review of the diatheses and the temperaments of adolescents, the pathogenesis of the common dystrophies, their diagnosis and treatment.

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